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(54) Title: PHARMACEUTICALLY ACTIVE COMPOUNDS AND METHODS OF USE

(57) Abstract: The invention provides substituted pyrazole compounds, and methods of treatment and pharmaceutical compositions that utilize or comprise one or more such compounds. Compounds of the invention are useful for the treatment of mammalian infertility.



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## 5 PHARMACEUTICALLY ACTIVE COMPOUNDS AND METHODS OF USE

The present application claims the benefit of U.S. provisional application number 60/205,814, filed May 19, 2000, incorporated herein by reference in its entirety.

10

## BACKGROUND OF THE INVENTION

## 1. Field of the Invention

The present invention relates to substituted pyrazole compounds, and methods of treatment and pharmaceutical compositions that utilize or comprise one or more such compounds. Compounds of the invention are useful for the treatment of mammalian infertility.

15

## 2. Background

Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH) are produced by the anterior pituitary gland and are involved in mammalian reproductive processes. The glycoprotein family of pituitary hormones such as FSH, LH and the thyrotropic hormone (TSH) contain carbohydrate moieties and have common  $\alpha$ -subunit and distinct  $\beta$ -subunits (1-4) providing receptor recognition and specificity. These proteins are relatively large (28-38 kDa) heterodimeric glycoproteins.

25

LH is released from the anterior pituitary gland under the influence of gonadotropin releasing hormone and progesterones. In the female LH stimulates ovulation and is the major hormone involved in the regulation of progesterone secretion by the corpus luteum. In the male LH stimulates Leydig cells to secrete androgens, particularly testosterone.

30

FSH is released from the anterior pituitary under the influence of gonadotropin releasing hormone, oestrogens and from the placenta during pregnancy. FSH acts on the ovaries stimulating maturation of follicles and regulates secretion of oestrogens.

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In the male FSH is responsible for the integrity of the seminiferous tubules and acts on Sertoli cells to support gametogenesis.

The LH and FSH receptors belong to the family of G protein coupled  
5 receptors, which are complex transmembrane proteins characterized by seven hydrophobic helices. LH and FSH receptors also share close sequence homology (approximately 40%). The receptors' extracellular domains bind to their respective hormones with high affinity and specificity. The intracellular portion of FSH and LH  
10 receptors is coupled to a Gs protein. Upon receptor activation, the hormonal interaction with the extracellular domain results in a cascade of events that lead to specific biological effects of the gonadotropin.

LH and FSH have been used for treatment for female infertility and spermatogenesis disorders. See U.S. Patents 5,767,067; 5,639,639; and 5,017,557.  
15 ;

However, those therapies have some notable shortcomings. For instance, current FSH treatment is limited by lack of oral bioavailability, high costs and need of close medical personnel supervision throughout an administration protocol.

20 It thus would be desirable to have new agents and methods to treat infertility in mammals.

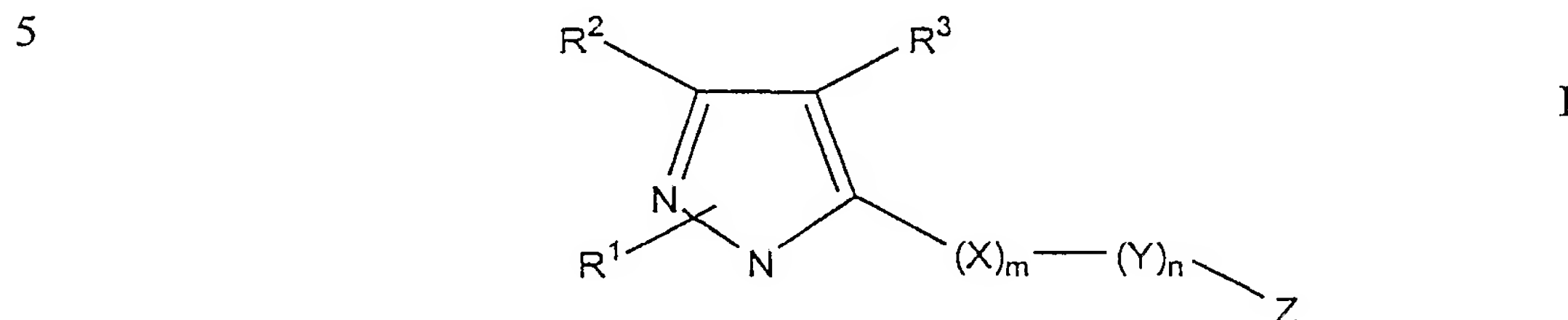
## SUMMARY OF THE INVENTION

We have now found that substituted pyrazole compounds are potent  
25 Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH) agonists. Compounds of the invention are particularly useful for treatment of infertility in mammals.

Pyrazole compounds of the invention are substituted by other than hydrogen in  
30 one or more pyrazole ring positions, and preferably are substituted at the 1, 3, 4 and/or 5 ring positions by a non-hydrogen substituent. Typical pyrazole compounds of the invention are substituted at least at the 5-ring position by other than hydrogen.

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Generally preferred for use in the therapeutic methods of the invention are substituted pyrazole compounds of the following Formula I:



10

wherein R<sup>1</sup> is hydrogen; optionally substituted alkyl preferably having 1 to about 20 carbons, more preferably 1 to about 12 carbons; optionally substituted alkenyl preferably having 2 to about 20 carbon atoms, more preferably 2 to about 12 carbon atoms; optionally substituted alkynyl preferably having 2 to about 20 carbon atoms, more preferably 2 to about 12 carbon atoms; optionally substituted carbocyclic aryl having at least about 6 ring carbon atoms; optionally substituted aralkyl having at least about 6 ring carbon atoms; optionally substituted heteroaromatic or heteroalicyclic group having 1 to 3 rings, 3 to 8 ring members in each ring and from 1 to 3 hetero atoms (N, O or S); or optionally substituted heteroaralkyl or heteroalicyclicalkyl group having from 1 to 3 rings, 3 to 8 ring members in each ring and from 1 to 3 hetero atoms (N, O or S);

R<sup>2</sup> and R<sup>3</sup> are each independently hydrogen, halogen, optionally substituted alkyl preferably having 1 to about 20 carbons, more preferably 1 to about 12 carbons; optionally substituted alkenyl preferably having 2 to about 20 carbon atoms, more preferably 2 to about 12 carbon atoms; optionally substituted alkynyl preferably having 2 to about 20 carbon atoms, more preferably 2 to about 12 carbon atoms; optionally substituted alkoxy preferably having from 1 to about 20 carbon atoms, more preferably 1 to about 12 carbon atoms; optionally substituted alkylthio preferably having from 1 to about 20 carbon atoms, more preferably 1 to about 12 carbon atoms; optionally substituted alkylsulfinyl preferably having from 1 to about 20 carbon atoms, more preferably 1 to about 12 carbon atoms; optionally substituted alkylsulfonyl preferably having from 1 to about 20 carbon atoms, more preferably 1 to about 12 carbon atoms; optionally substituted carbocyclic aryl having at least about 6



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ring carbon atoms; optionally substituted aralkyl having at least about 6 ring carbon atoms; optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 ring members in each ring and from 1 to 3 hetero atoms (particularly 1-3 N, O and/or S atoms); or optionally substituted heteroaralkyl or heteroalicyclicalkyl group having from 1 to 3 rings, 3 to 8 ring members in each ring and from 1 to 3 hetero atoms (particularly 1-3 N, O and/or S atoms);

wherein preferably at least one of  $R^1$ ,  $R^2$  and  $R^3$  are other than hydrogen and more preferably at least two of  $R^1$ ,  $R^2$  and  $R^3$  are other than hydrogen;

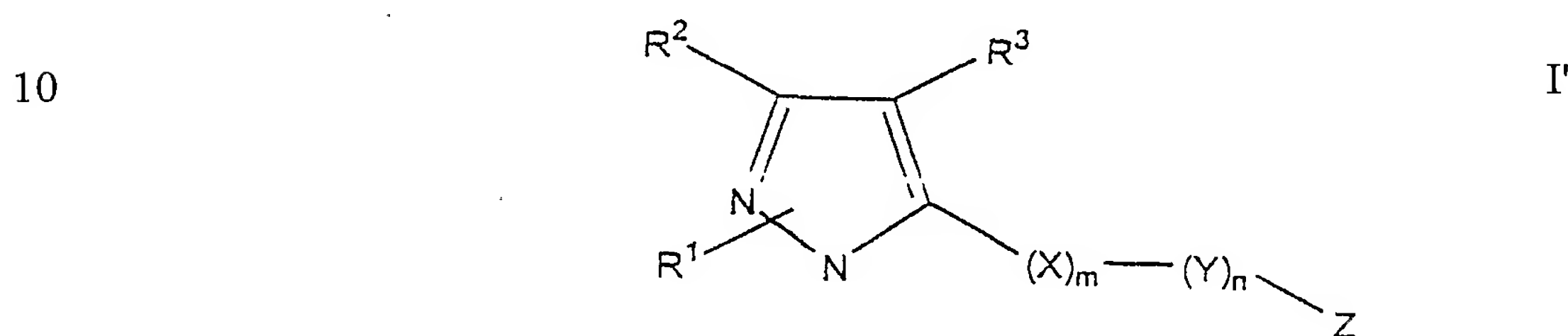
X is optionally substituted alkylene preferably having 1 to about 12 chain carbons, more preferably 2 to about 8 chain carbons, still more preferably 3 to about 6 alkylene chain carbons; optionally substituted alkenylene preferably having 2 to about 12 chain carbons, more preferably 2 to about 8 chain carbons, still more preferably 3 to about 6 alkenylene chain carbons; optionally substituted alkynylene preferably having 2 to about 12 chain carbons, more preferably 2 to about 8 chain carbons, still more preferably 3 to about 6 alkynylene chain carbons; optionally substituted heteroalkylene preferably having 1 to about 12 chain carbons, more preferably 2 to about 8 chain carbons, still more preferably 3 to about 6 heteroalkylene chain carbons and a total of 4 or 5 atoms in the heteroalkylene chain inclusive of hetero atoms (particularly N, O and/or S atoms); optionally substituted heteroalkenylene preferably having 2 to about 12 chain carbons, more preferably 2 to about 8 chain carbons, still more preferably 3 to about 6 heteroalkenylene chain carbons and a total of 4 or 5 atoms in the heteroalkenylene chain (particularly N, O and/or S atoms); optionally substituted heteroalkynylene preferably having 2 to about 12 chain carbons, more preferably 2 to about 8 chain carbons, still more preferably 4 or 5 heteroalkynylene chain carbons and a total of 4 or 5 atoms in the heteroalkynylene chain inclusive of hetero atoms (particularly N, O and/or S atoms); or X is optionally alicyclic, optionally substituted carbocyclic aryl; optionally substituted heteroalicyclic, optionally substituted heteroaromatic, optionally substituted heteroaralkyl, or optionally substituted heteroalicyclicalkyl group, each preferably having 3-10 carbon or hetero atoms in a ring, more preferably 5 or 6 membered ring(s), and 1-3 N, O or S atoms;

Y is optionally substituted amino; optionally substituted methylene (e.g. unsubstituted methylene,  $\text{CH}_2$ ), carbonyl ( $\text{C}=\text{O}$ ); or sulfonyl ( $\text{SO}_2$ );

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Z is an optionally substituted alkylamine; an amino acid (natural or non-natural amino acid) including a  $\beta$ -amino acid; or a glycine; or a derivative thereof, attached to the rest of the molecule either by its amino or carboxylic acid residue depending on the nature of Y; m is 0 (where no X group is present) or 1, and preferably m is 1; n is 0 (where no Y group is present) or 1, and preferably n is 1; and pharmaceutically acceptable salts thereof.

Preferred compounds of Formula I include those of the following Formula I':



15        wherein  $R^1$ ,  $R^2$  and  $R^3$  are each independently hydrogen; optionally substituted alkyl preferably having 1 to about 20 carbons, more preferably 1 to about 12 carbons; optionally substituted alkenyl preferably having 2 to about 20 carbon atoms, more preferably 2 to about 12 carbon atoms; optionally substituted alkynyl preferably having 2 to about 20 carbon atoms, more preferably 2 to about 12 carbon atoms; optionally substituted alkoxy preferably having 1 to about 20 carbon atoms, more preferably 1 to about 12 carbon atoms; optionally substituted alkylthio preferably having 1 to about 20 carbon atoms, more preferably 1 to about 12 carbon atoms; optionally substituted alkylsulfinyl preferably having 1 to about 20 carbon atoms, more preferably 1 to about 12 carbon atoms; optionally substituted alkylsulfonyl preferably having 1 to about 20 carbon atoms, more preferably 1 to about 12 carbon atoms; optionally substituted carbocyclic aryl having at least 6 ring carbon atoms; optionally substituted aralkyl having at least 6 ring atoms; optionally substituted heteroaromatic or heteroalicyclic group having 1 to 3 rings, 3 to 8 ring members in each ring and from 1 to 3 hetero atoms (N, O or S); or optionally substituted heteroaralkyl or heteroalicyclicalkyl having 1 to 3 rings, 3 to 8 ring members in each ring and from 1 to 3 hetero atoms (particularly N, O or S);

30        X is optionally substituted alkylene preferably having 1 to about 12 chain carbons, more preferably 2 to about 8 chain carbons, still more preferably 3 to about 6

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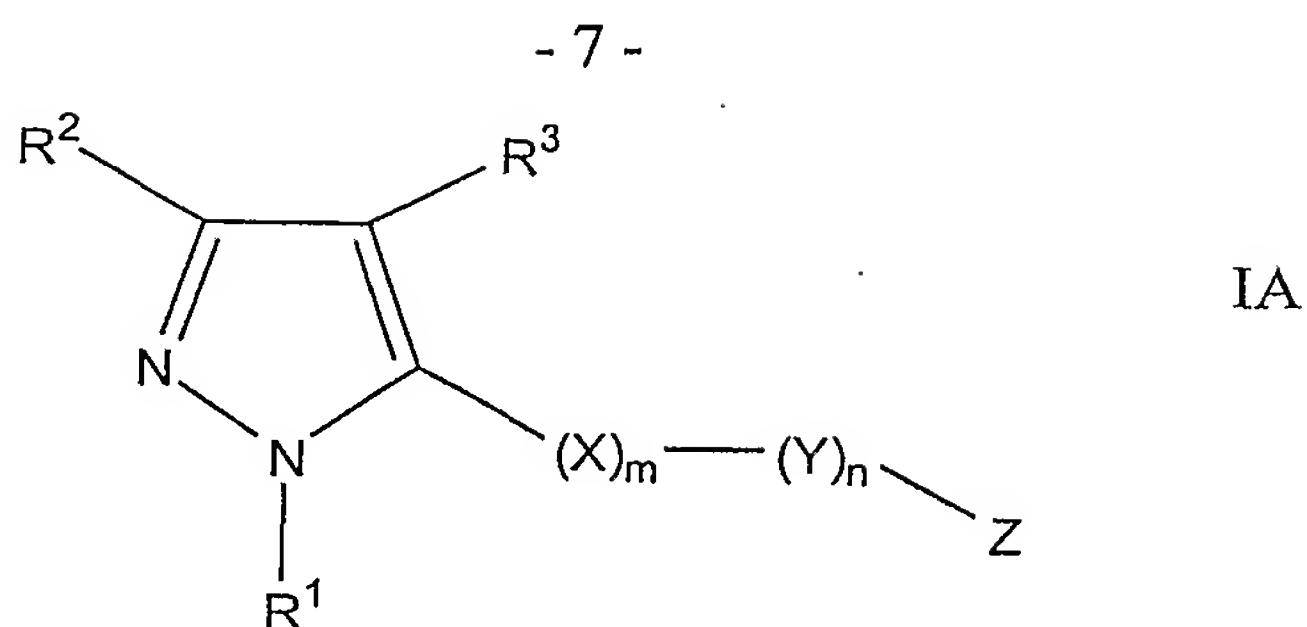
alkylene chain carbons; optionally substituted alkenylene preferably having 2 to about 12 chain carbons, more preferably 2 to about 8 chain carbons, still more preferably 3 to about 6 alkenylene chain carbons; optionally substituted alkynylene preferably having 2 to about 12 chain carbons, more preferably 2 to about 8 chain carbons, still more preferably 3 to about 6 alkynylene chain carbons; optionally substituted heteroalkylene preferably having 1 to about 12 chain carbons, more preferably 1 to about 8 chain carbons, still more preferably 3 to about 6 heteroalkynylene chain carbons and a total of 4 or 5 atoms in the heteroalkylene chain (inclusive of N, O or S atoms); optionally substituted heteroalkenylene preferably having 2 to about 12 chain carbons, more preferably 2 to about 8 chain carbons, still more preferably 3 to about 6 heteroalkenylene chain carbons and a total of 4 or 5 atoms in the heteroalkenylene chain (inclusive of N, O or S atoms); optionally substituted heteroalkynynylene preferably having 2 to about 12 chain carbons, more preferably 2 to about 8 chain carbons, still more preferably 3 to about 6 heteroalkynylene chain carbons and a total of 4 or 5 atoms in the heteroalkynylene chain (inclusive of N, O or S atoms);

or X is optionally substituted alicyclic; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic; optionally substituted heteroalicyclic group; optionally substituted heteroaralkyl; or optionally substituted heteroalicyclicalkyl group, each preferably having 3 to 10 carbon or hetero (N, O or S) atoms in a ring, more preferably 5 or 6 membered ring(s), and 1-3 N, O or S atoms;

Y is optionally substituted amino; optionally substituted methylene; carbonyl; or sulfonyl;

Z is an optionally substituted alkylamine; an amino acid (natural or non-natural amino acid) including a  $\beta$ -amino acid; or a glycine; m is 0 (where no X group is present) or 1, and preferably m is 1; n is 0 (where no Y group is present) or 1, and preferably n is 1; and pharmaceutically acceptable salts thereof.

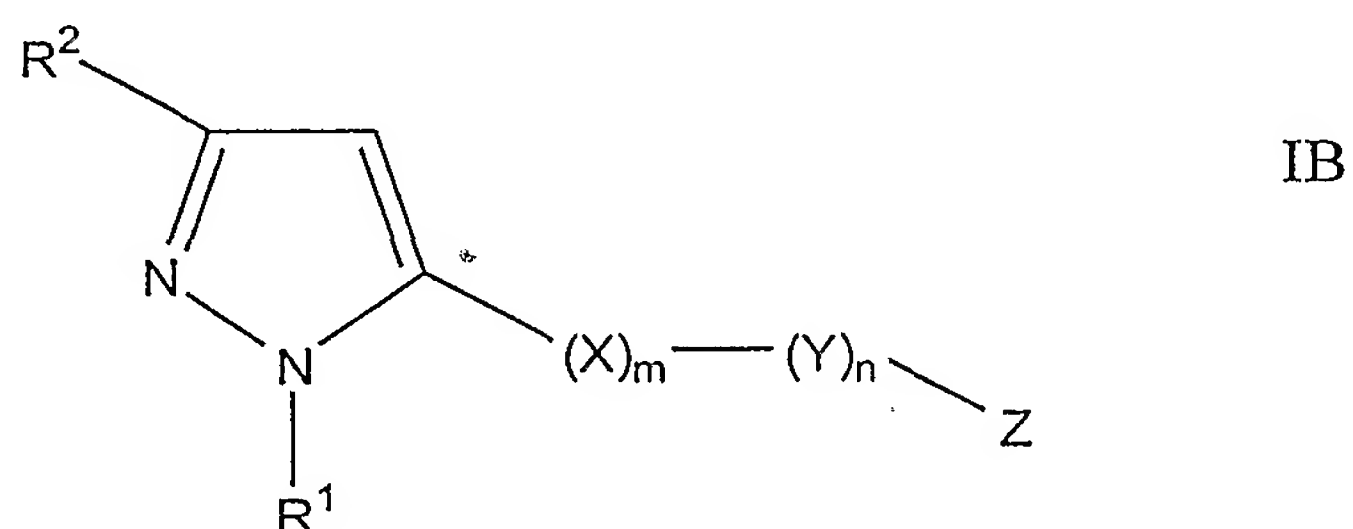
Preferred compounds of Formula I also include those where the pyrazole ring nitrogen has a non-hydrogen substituent, such as compounds of the following Formula IA:



wherein R<sup>1</sup> is a non-hydrogen substituent selected from the same group as defined for R<sup>1</sup> in Formula I above; R<sup>2</sup>, R<sup>3</sup>, X, Y, Z, m and n are the same as defined in Formula I above; and pharmaceutically acceptable salts thereof.

Preferred R<sup>1</sup> groups of compounds of Formula IA include optionally substituted alkyl; optionally substituted alkenyl; optionally substituted carbocyclic aryl; optionally substituted aryalkyl; optionally substituted heteroaromatic; optionally substituted heteroalicyclic group; optionally substituted heteroarylalkyl; or optionally substituted heteroalicyclicalkyl group.

Preferred compounds of the invention also include those having a non-hydrogen substituent at the pyrazole 1- and 3-positions, such as compounds of the following Formula IB:



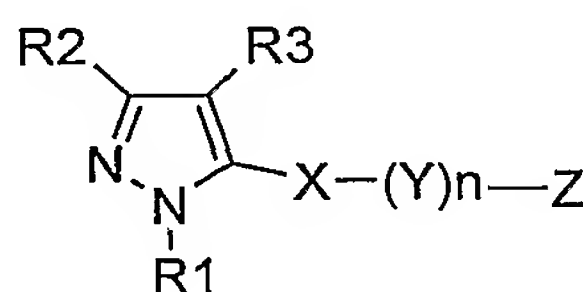
wherein R<sup>1</sup> and R<sup>2</sup> are each non-hydrogen substituents independently selected from the same group as defined for R<sup>1</sup> and R<sup>2</sup> in Formula I above; X, Y, Z, m and n are the same as defined in Formula I above; and pharmaceutically acceptable salts thereof.

Preferred R<sup>1</sup> groups of compounds of Formula IB include optionally substituted alkyl; optionally substituted alkenyl; optionally substituted carbocyclic aryl; optionally substituted aryalkyl; optionally substituted heteroaromatic; optionally

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substituted heteroalicyclic group; optionally substituted heteroarylakyl; or optionally substituted heteroalicyclicalkyl group.

Preferred compounds of the invention also include those having a non-  
 5 hydrogen substituent at the pyrazole 1- and 3-positions, such as compounds of the following Formula IC:



IC

10 wherein R<sup>1</sup> and R<sup>2</sup> are each non-hydrogen substituents independently selected from the same group as defined in Formula I above;

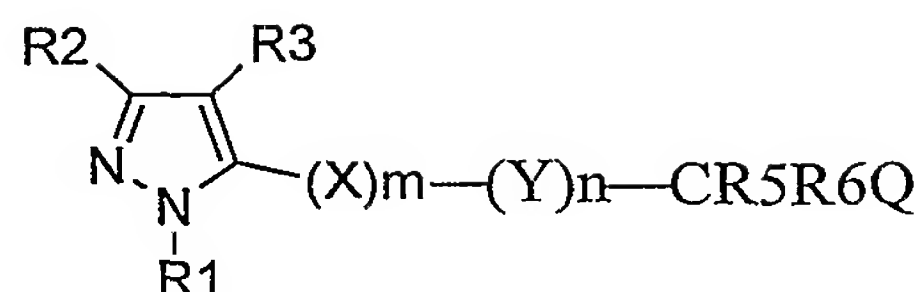
R<sup>3</sup>, Y, Z, and n are the same as defined in Formula I above;

X is optionally substituted heteroalkylene preferably having 1 to about 12 chain carbons, more preferably 2 to about 8 chain carbons, still more preferably 3 to  
 15 about 6 heteroalkylene chain carbons and a total of 4 or 5 atoms in the heteroalkylene chain inclusive of N, O and/or S atoms; optionally substituted heteroalkenylene preferably having 2 to about 12 chain carbons, more preferably 2 to about 8 chain carbons, still more preferably 3 to about 6 heteroalkenylene chain carbons and a total of 4 or 5 atoms in the heteroalkenylene chain inclusive of N, O or S atoms; optionally  
 20 substituted heteroalkynynylene preferably having 2 to about 12 chain carbons, more preferably 2 to about 8 chain carbons, still more preferably 4 or 5 heteroalkynylene chain carbons and a total of 4 or 5 atoms in the heteroalkynylene chain inclusive of N, O or S atoms; and pharmaceutically acceptable salts thereof.

25 Preferred compounds of the invention also include those having a non-hydrogen substituent at the pyrazole 1- and 3-positions, such as compounds of the following Formula ID



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ID

wherein R<sup>1</sup> and R<sup>2</sup> are each non-hydrogen substituents independently selected  
 5 from the same group as defined in Formula I above;

R<sup>3</sup>, X, Y, m and n are the same as defined in Formula I above;

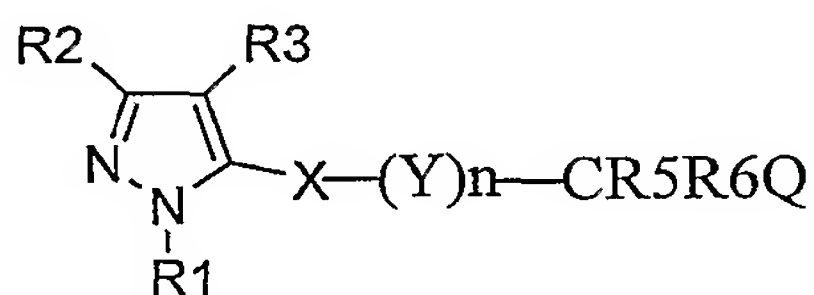
R<sup>5</sup> and R<sup>6</sup> are independently hydrogen, optionally substituted alkyl preferably  
 having 1 to about 20 carbons, more preferably 1 to about 12 carbons; optionally  
 substituted alkenyl preferably having 2 to about 20 carbon atoms, more preferably 2 to  
 10 about 12 carbon atoms; optionally substituted alkynyl preferably having 2 to about 20  
 carbon atoms, more preferably 2 to about 12 carbon atoms; optionally substituted  
 carbocyclic aryl having at least about 6 ring carbon atoms; optionally substituted  
 aralkyl having at least about 6 ring carbon atoms; optionally substituted  
 heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 ring members  
 15 in each ring and from 1 to 3 hetero atoms; or optionally substituted heteroaralkyl or  
 heteroalicyclicalkyl group having from 1 to 3 rings, 3 to 8 ring members in each ring  
 and from 1 to 3 hetero atoms more preferably one of R<sup>5</sup> and R<sup>6</sup> is hydrogen; and

Q is omitted (it does not exist) or is  $-(CH_2)_p-CO-A-R^7$  wherein p is 0, 1 or 2,  
 A is O or NH and R<sup>7</sup> is independently hydrogen, optionally substituted alkyl  
 20 preferably having 1 to about 20 carbons, more preferably 1 to about 12 carbons;  
 optionally substituted alkenyl preferably having 2 to about 20 carbon atoms, more  
 preferably 2 to about 12 carbon atoms; optionally substituted alkynyl preferably  
 having 2 to about 20 carbon atoms, more preferably 2 to about 12 carbon atoms;  
 optionally substituted carbocyclic aryl having at least about 6 ring carbon atoms;  
 25 optionally substituted aralkyl having at least about 6 ring carbon atoms; optionally  
 substituted heteroaromatic or heteroalicyclic group 1 to 3 rings, 3 to 8 ring members  
 in each ring and from 1 to 3 hetero atoms (particularly 1-3 N, O and/or S atoms); or  
 optionally substituted heteroaralkyl or heteroalicyclicalkyl group having from 1 to 3  
 rings, 3 to 8 ring members in each ring and from 1 to 3 hetero atoms (particularly 1-3  
 30 N, O and/or S atoms); and pharmaceutically acceptable salts thereof.

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Preferred compounds of the invention also include those having a non-hydrogen substituent at the pyrazole 1- and 3-positions, such as compounds of the following Formula IE

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IE

wherein  $\text{R}^1$  and  $\text{R}^2$  are each non-hydrogen substituents independently selected from the same group as defined in Formula I above;  $\text{R}^3$ , Y and n are the same as defined in Formula I above; X is optionally substituted heteroalkylene preferably having 1 to about 12 chain carbons, more preferably 2 to about 8 chain carbons, still more preferably 3 to about 6 heteroalkylene chain carbons and a total of 4 or 5 atoms in the heteroalkylene chain inclusive of N, O and/or S atoms; optionally substituted heteroalkenylene preferably having 2 to about 12 chain carbons, more preferably 2 to about 8 chain carbons, still more preferably 3 to about 6 heteroalkenylene chain carbons and a total of 4 or 5 atoms in the heteroalkenylene chain inclusive of N, O and/or S atoms; optionally substituted heteroalkynynylene preferably having 2 to about 12 chain carbons, more preferably 2 to about 8 chain carbons, still more preferably 4 or 5 heteroalkynylene chain carbons and a total of 4 or 5 atoms in the heteroalkynylene chain inclusive of N, O and/or S atoms;

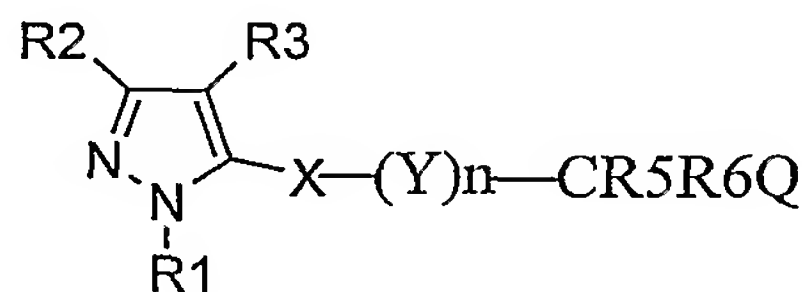
$\text{R}^5$  and  $\text{R}^6$  are independently hydrogen, optionally substituted alkyl preferably having 1 to about 20 carbons, more preferably 1 to about 12 carbons; optionally substituted alkenyl preferably having 2 to about 20 carbon atoms, more preferably 2 to about 12 carbon atoms; optionally substituted alkynyl preferably having 2 to about 20 carbon atoms, more preferably 2 to about 12 carbon atoms; optionally substituted carbocyclic aryl having at least about 6 ring carbon atoms; optionally substituted aralkyl having at least about 6 ring carbon atoms; optionally substituted heteroaromatic or heteroalicyclic group 1 to 3 rings, 3 to 8 ring members in each ring and from 1 to 3 hetero atoms (particularly 1-3 N, O and/or S atoms); or optionally substituted heteroaralkyl or heteroalicyclicalkyl group having from 1 to 3 rings, 3 to 8

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ring members in each ring and from 1 to 3 hetero atom (particularly 1-3 N, O and/or S atoms), more preferably one of R<sup>5</sup> and R<sup>6</sup> is hydrogen; and

Q is omitted (i.e. it is not present) or is  $-(CH_2)_p-CO-A-R^7$  wherein p is 0, 1 or 2 ; A is O or NH and R<sup>7</sup> is independently hydrogen , optionally substituted alkyl preferably having 1 to about 20 carbons, more preferably 1 to about 12 carbons; optionally substituted alkenyl preferably having 2 to about 20 carbon atoms, more preferably 2 to about 12 carbon atoms; optionally substituted alkynyl preferably having 2 to about 20 carbon atoms, more preferably 2 to about 12 carbon atoms; optionally substituted carbocyclic aryl having at least about 6 ring carbon atoms; optionally substituted aralkyl having at least about 6 ring carbon atoms; optionally substituted heteroaromatic or heteroalicyclic group 1 to 3 rings, 3 to 8 ring members in each ring and from 1 to 3 hetero atoms (particularly 1-3 N, O and/or S atoms); or optionally substituted heteroaralkyl or heteroalicyclicalkyl group having from 1 to 3 rings, 3 to 8 ring members in each ring and from 1 to 3 hetero atoms (particularly 1-3 N, O and/or S atoms); and pharmaceutically acceptable salts thereof.

Preferred compounds of the invention also include those having a non-hydrogen substituent at the pyrazole 1- and 3-positions, such as compounds of the following Formula IF:



IF

wherein R<sup>1</sup> and R<sup>2</sup> are each non-hydrogen substituents independently selected from the same group as defined in Formula I above;

R<sup>3</sup>, Y and n are the same as defined in Formula I above;

X is optionally alicyclic, optionally substituted carbocyclic aryl; optionally substituted heteroalicyclic, optionally substituted heteroaromatic, optionally substituted heteroaralkyl, or optionally substituted heteroalicyclicalkyl group, each preferably having 3-10 carbon or hetero atoms in a ring, more preferably 5 or 6

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membered ring(s), and 1-3 N, O or S atoms; R<sup>5</sup> and R<sup>6</sup> are independently hydrogen , optionally substituted alkyl preferably having 1 to about 20 carbons, more preferably 1 to about 12 carbons; optionally substituted alkenyl preferably having 2 to about 20 carbon atoms, more preferably 2 to about 12 carbon atoms; optionally substituted  
5 alkynyl preferably having 2 to about 20 carbon atoms, more preferably 2 to about 12 carbon atoms; optionally substituted carbocyclic aryl having at least about 6 ring carbon atoms; optionally substituted aralkyl having at least about 6 ring carbon atoms; optionally substituted heteroaromatic or heteroalicyclic group 1 to 3 rings, 3 to 8 ring members in each ring and from 1 to 3 hetero atoms (particularly 1-3 N, O and/or S  
10 atoms); or optionally substituted heteroaralkyl or heteroalicyclicalkyl group having from 1 to 3 rings, 3 to 8 ring members in each ring and from 1 to 3 hetero atoms (particularly 1-3 N, O and/or S atoms), more preferably one of R<sup>5</sup> and R<sup>6</sup> is hydrogen; and

Q is omitted (it does not exist) or is  $-(CH_2)_p-CO-A-R^7$  wherein p is 0, 1 or 2 ;  
15 A is O or NH and R<sup>7</sup> is independently hydrogen , optionally substituted alkyl preferably having 1 to about 20 carbons, more preferably 1 to about 12 carbons; optionally substituted alkenyl preferably having 2 to about 20 carbon atoms, more preferably 2 to about 12 carbon atoms; optionally substituted alkynyl preferably having 2 to about 20 carbon atoms, more preferably 2 to about 12 carbon atoms;  
20 optionally substituted carbocyclic aryl having at least about 6 ring carbon atoms; optionally substituted aralkyl having at least about 6 ring carbon atoms; optionally substituted heteroaromatic or heteroalicyclic group 1 to 3 rings, 3 to 8 ring members in each ring and from 1 to 3 hetero atoms; (particularly 1-3 N, O and/or S atoms); or optionally substituted heteroaralkyl or heteroalicyclicalkyl group having from 1 to 3  
25 rings, 3 to 8 ring members in each ring and from 1 to 3 hetero atoms (particularly 1-3 N, O and/or S atoms); and pharmaceutically acceptable salts thereof

Preferred R<sup>1</sup> groups of pyrazole compounds of Formulae I, I', IA, IB, IC, ID, IE and IF are optionally substituted alkyl, optionally substituted carbocyclic aryl,  
30 optionally substituted aralkyl (or aryalkyl) such as optionally substituted benzyl, and optionally substituted heteroaromatic, particularly optionally substituted phenyl, benzyl, pyridyl and naphthyl. Generally preferred R<sup>1</sup> groups include C<sub>1-16</sub> alkyl, branched alkyl such as propyl, butyl, pentyl, and the like, particularly branched alkyl

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such as i-propyl, t-butyl, sec-pentyl and the like, and optionally substituted phenyl such as phenyl having one or more C<sub>1-16</sub> alkyl substituents e.g. propyl, butyl including t-butyl, and the like. Particularly preferred R<sup>1</sup> groups have more significant size (molecular volume) such as C<sub>4-16</sub> alkyl preferably branched such as t-butyl, isopentyl and the like, and substituted carbocyclic aryl, particularly with branched ring substituents such phenyl substituted with t-butyl, isopentyl, trifluoromethyl, CF<sub>3</sub>CH<sub>2</sub>-, and the like.

Preferred R<sup>2</sup> groups of compounds of Formulae I, I', IA, IB, IC, ID, IE and IF include optionally substituted carbocyclic aryl, particularly optionally substituted phenyl and naphthyl, and optionally substituted heteroaromatic and heteroalicyclic, particularly nitrogen-containing heterocyclics such as pyridyl, tetrahydropyridyl, quinoline, isoquinoline, piperidine and the like.

Preferred X linker groups of compounds of Formulae I, I', IA, IB and ID are alkylene groups, particularly alkylene groups having 2, 3, 4, 5, or 6 chain carbon atoms (i.e. -CH<sub>2</sub>-), more preferably 4 or 5 chain carbon atoms. Preferred X linker groups of compounds of Formula I, I' IA, IB and ID include carbocyclic aryl, heteroaromatic, alicyclic and heteroalicyclic groups, particularly groups having 3 to 10 ring members, more particularly 4-6 membered rings, such as optionally substituted phenyl, thienyl, furyl, pyrrolyl and pyridyl groups. Carbonyl is a preferred Y group.

Preferred Z groups of compounds of Formulae I, I', IA, IB, IC, ID, IE and IF comprise hydroxy moieties, particularly phenolic moieties. Substituted amines and natural and non-natural amino acids are generally preferred Z groups. For example, preferred Z groups include optionally substituted C<sub>1-12</sub> alkylamine, preferably substituted with a phenolic group on the alkyl chain, such as -NH(CH<sub>2</sub>)<sub>1-8</sub>C<sub>6</sub>H<sub>4</sub>OH. Preferred Z groups include tyrosine groups and other aminophenyl groups such as -NHCH(CH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>OH)C(=O)NH<sub>2</sub>; -NH{CH<sub>2</sub>C<sub>6</sub>H<sub>3</sub>-(N=C-NH-)}C(=O)NH<sub>2</sub>; NH{CH<sub>2</sub>C<sub>6</sub>H<sub>3</sub>-(N=N-NH-)}C(=O)NH<sub>2</sub> where in such groups the phenolic moiety may be substituted at any available phenyl ring position, and preferably the hydroxyl is a meta or para substituent. Specifically preferred Z groups including tyrosine, homo-



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tyrosine, 4-hydroxy- $\alpha$ -phenylglycine, 4-amino-phenylalanine, 4-hydroxymethyl-phenylalanine, 4-acetyl-amino-phenylalanine, meta-tyrosine,  $\beta$ -homo-tyrosine, threonine, serine, and 4-hydroxy-phenyl-ethylamine.

5 Also, unless otherwise indicated herein, it is understood that the above Formulae I, I' IA, IB, IC, ID, IE and IF are inclusive of all possible regio isomers of the depicted pyrazoles, even in the case of Formulae IA, IB, IC, ID, IE and IF where the preferred regio isomer is depicted.

10 Particular compounds of the invention include:

N-{5-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]pentanoyl}tyrosinamide;  
 N-{5-[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]pentanoyl}tyrosinamide;  
 N-{5-[1-(4-tert-butylphenyl)-5-pyridin-3-yl-1H-pyrazol-3-yl]pentanoyl}tyrosinamide;  
 N-{5-[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]pentanoyl}tyrosinamide;  
 15 N-{5-[1-(4-tert-butylphenyl)-5-pyridin-4-yl-1H-pyrazol-3-yl]pentanoyl}tyrosinamide;  
 N-{5-[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]pentanoyl}-N,N-dimethyltyrosinamide;  
 N-(3-[1-(4-tert-butylphenyl)-5-pyridin-3-yl-1H-pyrazol-3-yl]propanoyl)tyrosinamide;  
 N-(3-[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]propanoyl)tyrosinamide  
 20 N-[4-(1-butyl-3-isoquinolin-3-yl-1H-pyrazol-5-yl)benzoyl]tyrosinamide;  
 N-{5-[1-(4-isopropylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]pentanoyl}tyrosinamide;  
 N-{6-[1-(4-isopropylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}tyrosinamide  
 N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}-3-hydroxyphenylalaninamide;  
 25 N-[1-(aminocarbonyl)-3-(4-hydroxyphenyl)propyl]-5-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]pentanamide;  
 N-[5-(1-butyl-3-isoquinolin-3-yl-1H-pyrazol-5-yl)pentanoyl]tyrosinamide;  
 N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}serinamide;  
 N-{6-[1-(4-iso-propylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}serinamide;  
 30 N-{6-[1-(4-iso-propylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}threonamide;  
 N-{5-[1-(4-isopropylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]pentanoyl}tyrosinamide;  
 6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]-N-[2-(4-hydroxyphenyl)ethyl]hexanamide;

- N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}tyrosinamide;  
 N-{5-[1-(4-tert-butylphenyl)-3-isoquinolin-3-yl-1H-pyrazol-5-yl]pentanoyl}tyrosinamide;  
 N-{6-[1-(4-tert-butylphenyl)-3-isoquinolin-3-yl-1H-pyrazol-5-yl]hexanoyl}tyrosinamide;  
 5 N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}-N-methyltyrosinamide;  
 N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}-4-(hydroxymethyl)phenylalaninamide;  
 10 4-amino-N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}phenylalaninamide;  
 4-(acetylamino)-N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}phenylalaninamide;  
 4-(aminocarbonyl)-N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}phenylalaninamide;  
 15 N-butyl-N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}tyrosinamide;  
 N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}threonamide;  
 N-[2-amino-1-(4-hydroxyphenyl)-2-oxoethyl]-6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanamide;  
 20 N-{2-[4-(aminosulfonyl)phenyl]ethyl}-5-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]pentanamide;  
 N-({5-[1-(4-isopropylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]thien-2-yl}carbonyl)tyrosinamide;  
 25 N-[2-amino-1-(4-hydroxyphenyl)-2-oxoethyl]-4-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]benzamide;  
 4-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]-N-[2-(4-hydroxyphenyl)ethyl]benzamide;  
 N-{3-[1-(4-tert-butylbenzyl)-3-isoquinolin-3-yl-1H-pyrazol-5-yl]benzoyl}tyrosinamide;  
 30 N-{5-[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]pentanoyl}tyrosinamide;  
 N-{3-[1-(4-tert-butylbenzyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]benzoyl}tyrosinamide;  
 N-{3-[1-(4-tert-butylphenyl)-3-isoquinolin-3-yl-1H-pyrazol-5-

- yl]benzoyl} tyrosinamide;
- N-[4-(1-butyl-3-isoquinolin-3-yl-1H-pyrazol-5-yl)benzoyl] tyrosinamide;
- N-{3-[1-(4-tert-butylbenzyl)-3-quinolin-3-yl-1H-pyrazol-5-yl]benzoyl} tyrosinamide;
- N-{3-[3-isoquinolin-3-yl-1-(4-propylphenyl)-1H-pyrazol-5-yl]benzoyl} tyrosinamide;
- 5 N-{5-[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]pentanoyl} tyrosinamide;
- N-{3-[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]benzoyl} tyrosinamide;
- N-{4-[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]benzoyl} tyrosinamide;
- N-{5-[1-(4-tert-butylbenzyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]pentanoyl} tyrosinamide;
- N-{3-[1-(4-tert-butylbenzyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]benzoyl} tyrosinamide;
- 10 N-{5-[1-(4-tert-butylbenzyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]pentanoyl} tyrosinamide;
- N-{5-[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]pentanoyl} tyrosinamide;
- N-[3-(1-butyl-3-isoquinolin-3-yl-1H-pyrazol-5-yl)benzoyl] tyrosinamide;
- N-(4-{[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]amino} butanoyl) tyrosinamide;
- 15 N-[(1-butyl-3-pyridin-3-yl-1H-pyrazol-5-yl)methyl]glycyl tyrosinamide;
- N-{[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]methyl} glycyl tyrosinamide;
- N-[(1-butyl-3-pyridin-3-yl-1H-pyrazol-5-yl)methyl]-beta-alanyl tyrosinamide;
- N-(3-{[(1-butyl-3-pyridin-3-yl-1H-pyrazol-5-yl)methyl]amino} benzoyl) tyrosinamide;
- 20 N-[3-({[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]methyl} amino) benzoyl] tyrosinamide;
- N-({1-[(1-butyl-3-pyridin-3-yl-1H-pyrazol-5-yl)methyl]piperidin-4-yl} carbonyl) tyrosinamide;
- N-[(1-{[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]methyl} piperidin-4-yl) carbonyl] tyrosinamide;
- 25 N-2--{[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]methyl}-N~1~- [2-(4-hydroxyphenyl)ethyl] glycineamide;
- N-3-[(1-butyl-3-pyridin-3-yl-1H-pyrazol-5-yl)methyl]-N~1~- [2-(4-hydroxyphenyl)ethyl]-beta-alanineamide;
- 30 4-{[(1-butyl-3-pyridin-3-yl-1H-pyrazol-5-yl)methyl]amino}-N-[2-(4-hydroxyphenyl)ethyl] benzamide; or an optically active isomer, racemate or tautomer thereof, and/or a pharmaceutically acceptable salts thereof.

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Additional preferred compound include:

- N-({3-[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]propoxy}acetyl)}tyrosinamide;
- 4-[2-({3-[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]propyl}amino)ethyl]phenol;
- 5 N-{3-[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]propyl}tyrosinamide;
- N-acetyl-N-{3-[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]propyl}tyrosinamide;
- N-({3-[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]propoxy}acetyl)tyrosinamide;
- 10 4-[2-({3-[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]propyl}amino)ethyl]phenol;
- N-{3-[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]propyl}tyrosinamide;
- N-acetyl-N-{3-[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]propyl}tyrosinamide;
- 15 3-[(4-{[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]amino}butanoyl)amino]-4-(4-hydroxyphenyl)butanamide;
- N-(4-{[1-(4-tert-butylphenyl)-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-pyrazol-5-yl]amino}butanoyl)tyrosinamide;
- 20 N-(3-{[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]amino}propyl)tyrosinamide;
- N-acetyl-N-(3-{[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]amino}propyl)tyrosinamide;
- N-(4-{[1-(4-tert-butylphenyl)-3-(1-oxidopyridin-4-yl)-1H-pyrazol-5-yl]amino}butanoyl)tyrosinamide;
- 25 4-{[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]amino}-N-[2-(4-hydroxyphenyl)ethyl]butanamide;
- 4-{2-[(4-{[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]amino}butyl)amino]ethyl}phenol;
- 30 N-(4-{[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]amino}butanoyl)-N-(2-hydroxyethyl)tyrosinamide;
- N-(4-{[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]amino}butanoyl)-N-[2-(1-methylpyrrolidin-2-yl)ethyl]tyrosinamide;

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- N-(4-{[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]amino}butanoyl)tyrosinamide;
- N-(4-{[1-(4-tert-butylphenyl)-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrazol-5-yl]amino}butanoyl)tyrosinamide;
- 5 (3R)-3-[(4-{[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]amino}butanoyl)amino]-4-(4-hydroxyphenyl)butanamide;
- N-(3-{[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]amino}propyl)tyrosinamide;
- N-acetyl-N-(3-{[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]amino}propyl)tyrosinamide;
- 10 N-(4-{[1-(4-tert-butylphenyl)-3-(1-oxidopyridin-3-yl)-1H-pyrazol-5-yl]amino}butanoyl)tyrosinamide;
- 4-{[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]amino}-N-[2-(4-hydroxyphenyl)ethyl]butanamide;
- 15 4-{2-[(4-{[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]amino}butyl)amino]ethyl}phenol;
- N-(4-{[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]amino}butanoyl)-N-(2-hydroxyethyl)tyrosinamide;
- N-(4-{[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]amino}butanoyl)-N-[2-
- 20 (1-methylpyrrolidin-2-yl)ethyl]tyrosinamide;
- N-(4-{[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]oxy}butanoyl)tyrosinamide; or an optically active isomer, racemate or tautomer thereof, and/or a pharmaceutically acceptable salts thereof.
- 25 Substituted pyrazole compounds of the invention are useful for treatment of infertility in male and female mammals, particularly humans. Therapeutic methods of the invention in general comprise administering an effective amount of one or more substituted pyrazole compounds as disclosed herein to a mammal in need thereof, such as a mammal suspected of suffering from infertility, particularly a human
- 30 suspected of suffering from infertility. Compounds of the invention will be useful for treatment of infertility conditions currently treated with FSH and/or LH, including female infertility and male spermatogenesis disorders.



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Additionally, in contrast to current protein therapeutics such as FSH, compounds of the invention can be administered orally and without extensive medical specialist supervision.

5 Preferred compounds of the invention exhibit good agonist activity in standard Follicle Stimulating Hormone (FSH) assays, such as the assay of Example 9 which follows.

10 It also has been found that substituted pyrazole compounds of the invention exhibit good inhibition activity against phosphodiesterase PDE4, adenosine transporters, and prostanoid receptors. Accordingly, methods are provided for treatment of diseases and disorders associated with phosphodiesterase PDE4, adenosine transporters, and prostanoid receptors, which methods in general comprise administration of an effective amount of one or more substituted pyrazole compounds  
15 to a patient (e.g. mammal, such as human or other primate) in need of such treatment.

The invention also provides pharmaceutical compositions that comprise one or more substituted pyrazole compounds of the invention and a suitable carrier for the compositions. Other aspects of the invention are disclosed *infra*.

20

## DETAILED DESCRIPTION OF THE INVENTION

We have now discovered that substituted pyrazole compounds, including compounds of the above Formulae I, I', IA, IB, IC, ID, IE and IF, that are useful for treatment of infertility in mammals, including female and male humans.

25

Suitable alkyl substituent groups of compounds of the invention (which includes compounds of Formulae I, I', IA, IB, IC, ID, IE and IF as defined above) typically have from 1 to about 12 carbon atoms, more preferably 1 to about 8 carbon atoms, still more preferably 1, 2, 3, 4, 5, or 6 carbon atoms. As used herein, the term  
30 alkyl unless otherwise modified refers to both cyclic and noncyclic groups, although of course cyclic groups will comprise at least three carbon ring members. Preferred alkenyl and alkynyl groups of compounds of the invention have one or more unsaturated linkages and typically from 2 to about 12 carbon atoms, more preferably 2

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to about 8 carbon atoms, still more preferably 2, 3, 4, 5, or 6 carbon atoms. The terms alkenyl and alkynyl as used herein refer to both cyclic and noncyclic groups, although straight or branched noncyclic groups are generally more preferred. Preferred alkoxy groups of compounds of the invention include groups having one or more oxygen

5 linkages and from 1 to about 12 carbon atoms, more preferably from 1 to about 8 carbon atoms, and still more preferably 1, 2, 3, 4, 5 or 6 carbon atoms. Preferred alkylthio groups of compounds of the invention include those groups having one or more thioether linkages and from 1 to about 12 carbon atoms, more preferably from 1 to about 8 carbon atoms, and still more preferably 1, 2, 3, 4, 5, or 6 carbon atoms.

10 Preferred alkylsulfinyl groups of compounds of the invention include those groups having one or more sulfoxide (SO) groups and from 1 to about 12 carbon atoms, more preferably from 1 to about 8 carbon atoms, and still more preferably 1, 2, 3, 4, 5, or 6 carbon atoms. Preferred alkylsulfonyl groups of compounds of the invention include those groups having one or more sulfonyl (SO<sub>2</sub>) groups and from 1 to about 12 carbon

15 atoms, more preferably from 1 to about 8 carbon atoms, and still more preferably 1, 2, 3, 4, 5 or 6 carbon atoms. Preferred aminoalkyl groups include those groups having one or more primary, secondary and/or tertiary amine groups, and from 1 to about 12 carbon atoms, more preferably 1 to about 8 carbon atoms, still more preferably 1, 2, 3, 4, 5, or 6 carbon atoms. Secondary and tertiary amine groups are generally more

20 preferred than primary amine moieties. Suitable heteroaromatic groups of compounds of the invention contain one or more N, O or S atoms and include, e.g., coumarinyl including 8-coumarinyl, quinolinyl including 8-quinolinyl, pyridyl, pyrazinyl, pyrimidyl, furyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, oxidizolyl, triazole, imidazolyl, indolyl, benzofuranyl and benzothiazole. Suitable heteroalicyclic groups of

25 compounds of the invention contain one or more N, O or S atoms and include, e.g., tetrahydrofuranyl, thienyl, tetrahydropyranyl, piperidinyl, morpholino and pyrrolidinyl groups. Suitable carbocyclic aryl groups of compounds of the invention include single and multiple ring compounds, including multiple ring compounds that contain separate and/or fused aryl groups. Typical carbocyclic aryl groups of

30 compounds of the invention contain 1 to 3 separate or fused rings and from 6 to about 18 carbon ring atoms. Specifically preferred carbocyclic aryl groups include phenyl; naphthyl including 1-naphthyl and 2-naphthyl; biphenyl; phenanthryl; anthracyl; and acenaphthyl. Substituted carbocyclic groups are particularly suitable including

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substituted phenyl, such as 2-substituted phenyl, 3-substituted phenyl, 4-substituted phenyl, 2,3-substituted phenyl, 2,4-substituted phenyl, and 2,4-substituted phenyl; and substituted naphthyl, including naphthyl substituted at the 5, 6 and/or 7 positions.

5           Suitable aralkyl groups of compounds of the invention include single and multiple ring compounds, including multiple ring compounds that contain separate and/or fused aryl groups. Typical aralkyl groups contain 1 to 3 separate or fused rings and from 6 to about 18 carbon ring atoms. Preferred aralkyl groups include benzyl and methylenenaphthyl (-CH<sub>2</sub>-naphthyl), and other carbocyclic aralkyl groups, as  
10   discussed above.

          Suitable heteroaralkyl groups of compounds of the invention include single and multiple ring compounds, including multiple ring compounds that contain separate and/or fused heteroaromatic groups, where such groups are substituted onto  
15   an alkyl linkage. More preferably, a heteroaralkyl group contains a heteroaromatic group that has 1 to 3 rings, 3 to 8 ring members in each ring and from 1 to 3 hetero (N, O or S) atoms, substituted onto an alkyl linkage. Suitable heteroaromatic groups substituted onto an alkyl linkage include e.g., coumarinyl including 8-coumarinyl, quinolinyl including 8-quinolinyl, pyridyl, pyrazinyl, pyrimidyl, furyl, pyrrolyl,  
20   thienyl, thiazolyl, oxazolyl, oxidizolyl, triazole, imidazolyl, indolyl, benzofuranyl and benzothiazole.

          Suitable heteroalicyclicalkyl groups of compounds of the invention include single and multiple ring compounds, where such groups are substituted onto an alkyl  
25   linkage. More preferably, a heteroalicyclicalkyl group contains at least one ring that has 3 to 8 ring members from 1 to 3 hetero (N, O or S) atoms, substituted onto an alkyl linkage. Suitable heteroalicyclic groups substituted onto an alkyl linkage include e.g. tetrahydrofuranyl, thienyl, tetrahydropyranyl, piperidinyl, morpholino and pyrrolidinyl groups.

30

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As discussed above, particularly preferred X linker groups are alkylene, particularly having 4 or 5 chain carbons, such as  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$  and  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$ . X linker groups may one contain one or more carbon-carbon double or triple bonds in the chain, i.e. a alkenylene, alkynylene, heteroalkenylene or heteroalkynylene linkage. Such unsaturated X groups typically contain 1, 2 or 3 carbon-carbon multiple bonds, more typically 1 or 2 carbon-carbon multiple bonds. An X group that is heteroalkylene, heteroalkenylene, or heteroalkynylene contains one or more N, O or S atoms in the linker chain, more typically 1 or 2 N, O or S atoms in the chain. An X linker group also preferably may be carbocyclic aryl or a heteroaromatic group, particularly 3-10 membered rings or fused rings, more particularly 4, 5 and 6 membered rings with zero, one or more N, O, or S atoms such as optionally substituted o-, m-, p-phenyl, pyridyl, furyl, thiophenyl and pyrrolidinyl rings.

As discussed above, R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, X, Y and Z groups are optionally substituted. A “substituted” R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, X, Y and Z group or other substituent may be substituted by other than hydrogen at one or more available positions, typically 1 to 3 or 4 positions, by one or more suitable groups such as those disclosed herein. Suitable groups that may be present on a “substituted” R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, X, Y and Z group or other substituent include e.g. halogen such as fluoro, chloro, bromo and iodo; cyano; hydroxyl; nitro; azido; alkanoyl such as a C<sub>1-6</sub> alkanoyl group such as acyl and the like; carboxamido; alkyl groups including those groups having 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5, or 6 carbon atoms; alkenyl and alkynyl groups including groups having one or more unsaturated linkages and from 2 to about 12 carbon, or 2, 3, 4, 5 or 6 carbon atoms; alkoxy groups having those having one or more oxygen linkages and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5 or 6 carbon atoms; aryloxy such as phenoxy; alkylthio groups including those moieties having one or more thioether linkages and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5 or 6 carbon atoms; alkylsulfinyl groups including those moieties having one or more sulfinyl linkages and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5, or 6 carbon atoms; alkylsulfonyl groups including those moieties having one or more sulfonyl linkages and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5, or 6 carbon atoms; aminoalkyl groups such as groups



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having one or more N atoms and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5 or 6 carbon atoms; carbocyclic aryl having 6 or more carbons, particularly phenyl (e.g. an R group being a substituted or unsubstituted biphenyl moiety); aralkyl having 1 to 3 separate or fused rings and from 6 to about 18 carbon ring atoms, with benzyl being a preferred group; aralkoxy having 1 to 3 separate or fused rings and from 6 to about 18 carbon ring atoms, with O-benzyl being a preferred group; or a heteroaromatic or heteroalicyclic group having 1 to 3 separate or fused rings with 3 to about 8 members per ring and one or more N, O or S atoms, e.g. coumarinyl, quinolinyl, pyridyl, pyrazinyl, pyrimidyl, furyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, imidazolyl, indolyl, benzofuranyl, benzothiazolyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, morpholino and pyrrolidinyl.

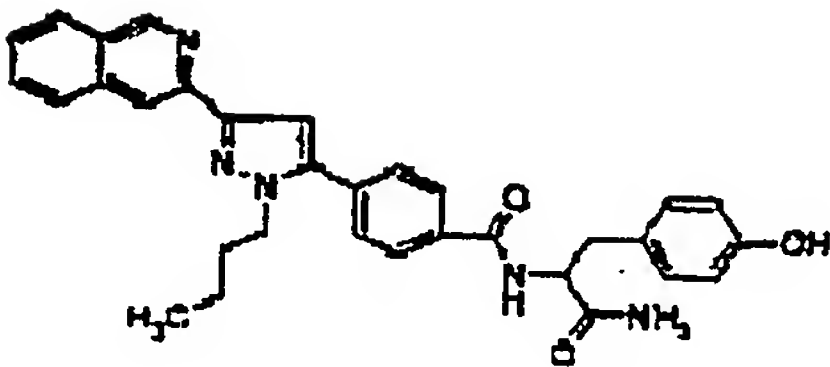
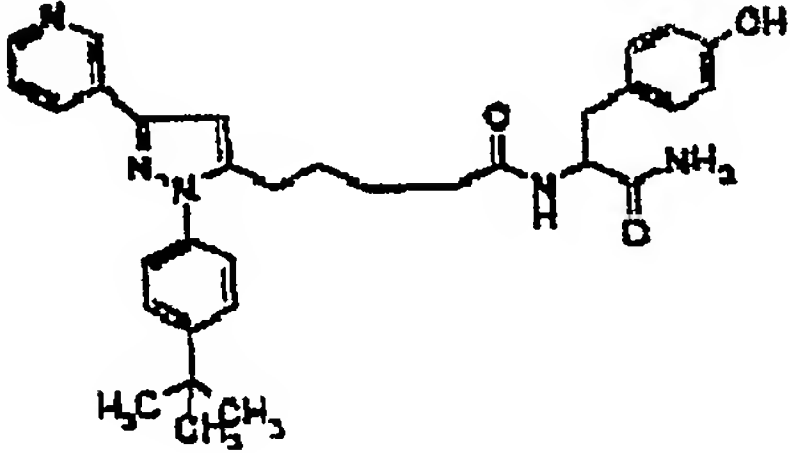
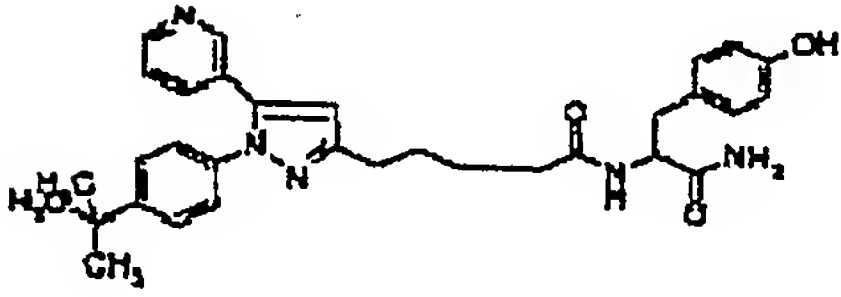
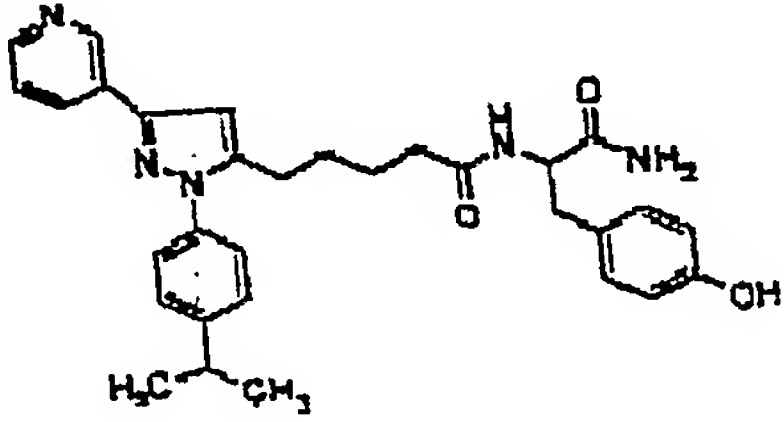
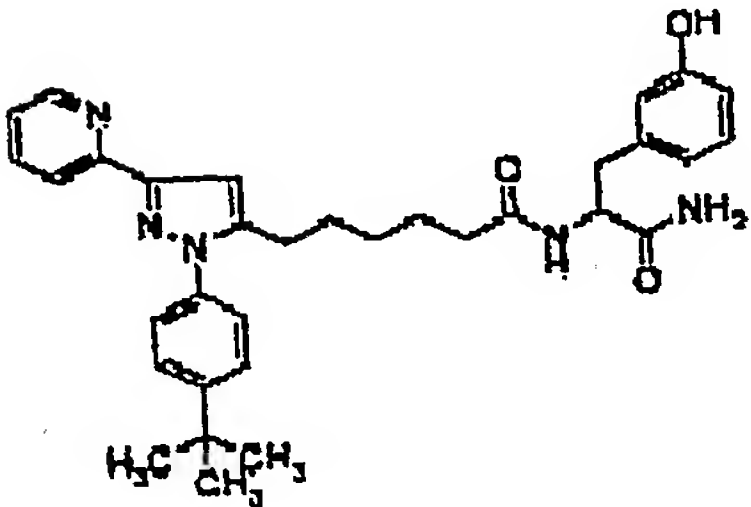
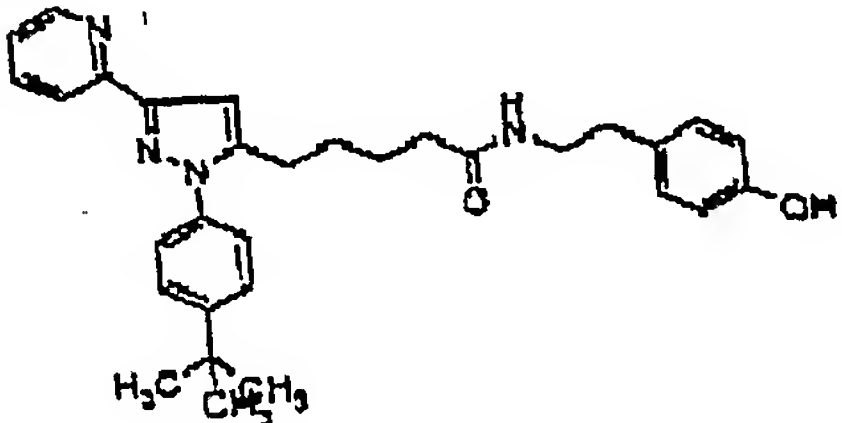
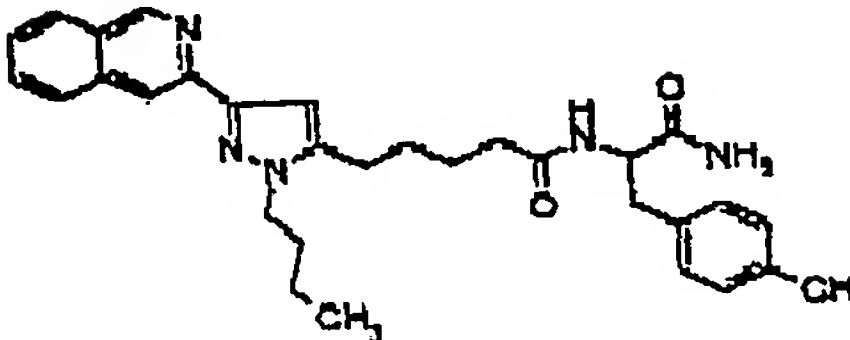
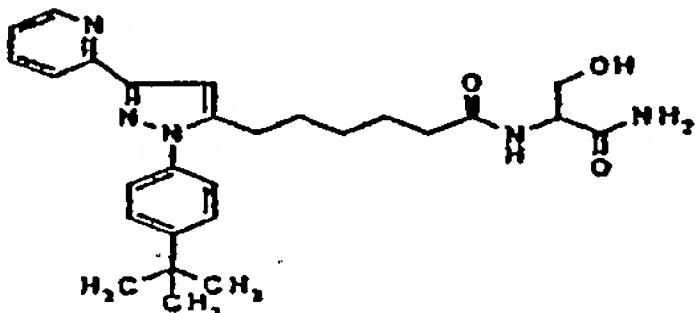
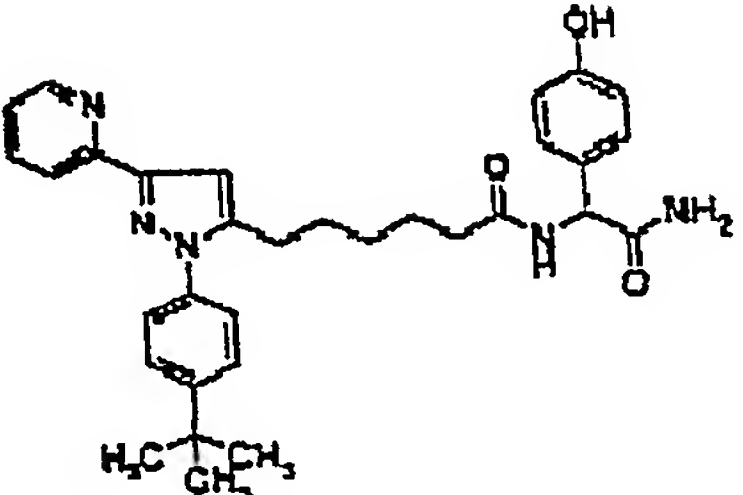
Preferred carbocyclic or heteroaromatic ring substituents of compounds of the invention include halogen (F, Cl, Br and I; hydroxyl; azido; optionally substituted alkyl having 1 to about 12 carbons such as methyl, ethyl, propyl and butyl and branched groups such as isopropyl, sec-butyl and tert-butyl, and including halogenated alkyl, particularly fluoro-alkyl having 1 to about 6 carbon atoms; optionally substituted alkoxy having 1 to about 12 carbons such as methoxy, ethoxy, propoxy and butoxy, and including halogenated alkoxy, particularly fluoro-alkoxy having 1 to about 6 carbon atoms; optionally substituted alkylthio having 1 to about 6 carbons such as methylthio and ethylthio; optionally substituted alkylsulfinyl having 1 to about 6 carbons such as methylsulfinyl ( $-S(O)CH_3$ ) and ethylsulfinyl ( $-S(O)CH_2CH_3$ ); optionally substituted alkylsulfonyl having 1 to about 6 carbons such as methylsulfonyl ( $-S(O)_2CH_3$ ) and ethylsulfonyl ( $-S(O)_2CH_2CH_3$ ); and optionally substituted arylalkoxy such as benzyloxy ( $C_6H_5CH_2O-$ ).

It should be understood that alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl and aminoalkyl substituent groups described above include groups where a hetero atom is directly bonded to a ring system, such as a carbocyclic aryl group or a heteroalicyclic or heteroaromatic group, as well as groups where a hetero atom of the group is spaced from such ring system by an alkylene linkage, e.g. of 1 to about 4 carbon atoms.



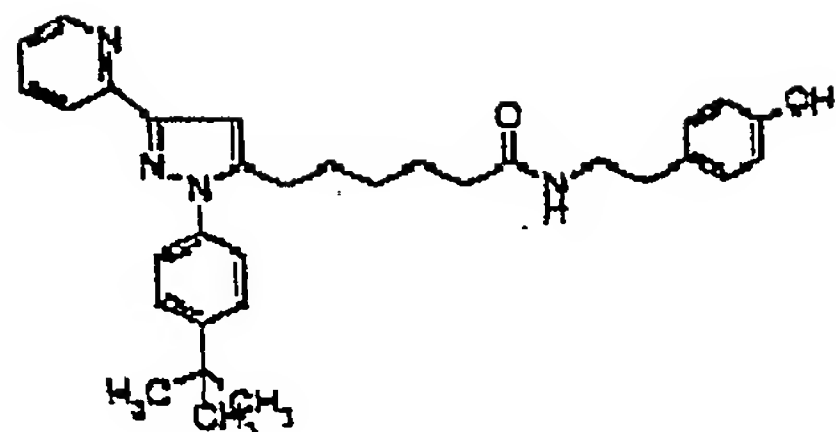
- 24 -

Specifically preferred compounds of the invention include the following depicted compounds, and pharmaceutically acceptable salts of these compounds. Results ( $EC_{50}$  values, expressed as  $\mu M$ ) for certain compounds in the FSH assay of Example 9 are set forth immediately right of the depicted compound structure.

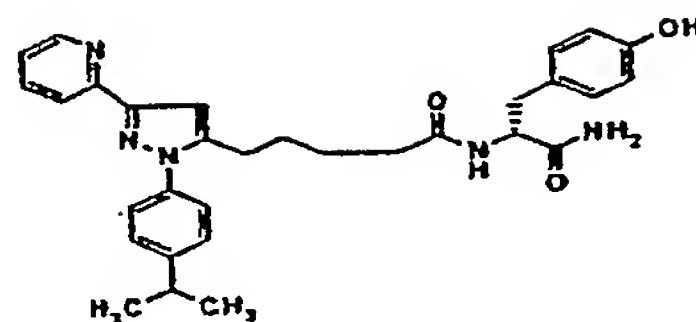
	<u><math>EC_{50}</math></u>		<u><math>EC_{50}</math></u>
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	0.525		0.144
	0.78		1.87
	1.13		3.25
			0.19

EC<sub>50</sub>

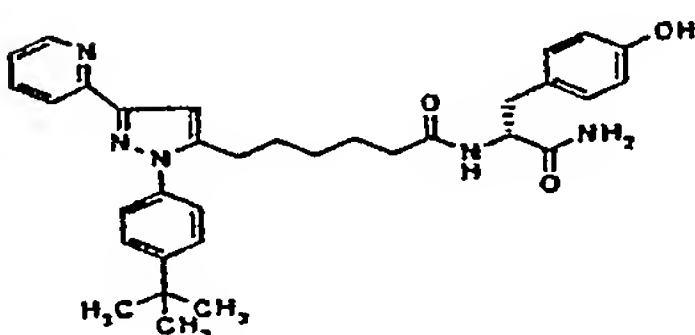
EC<sub>50</sub>



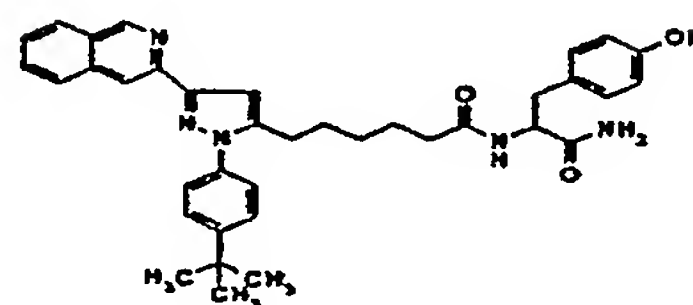
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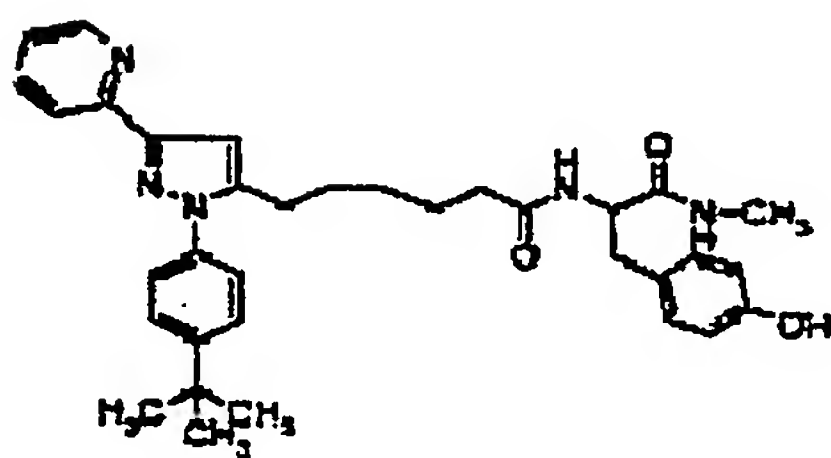
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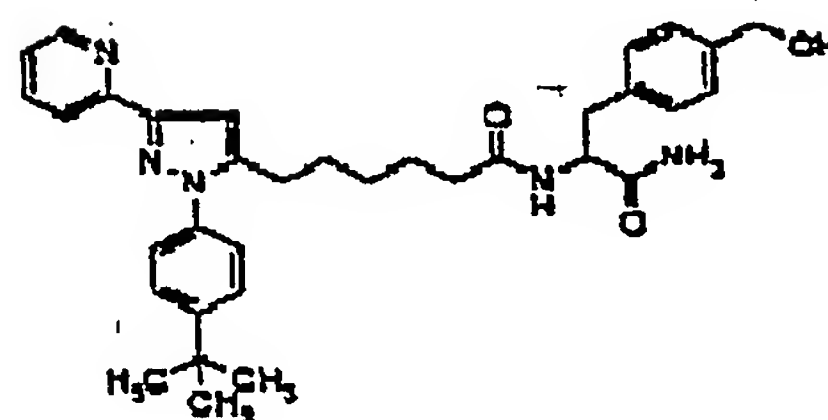
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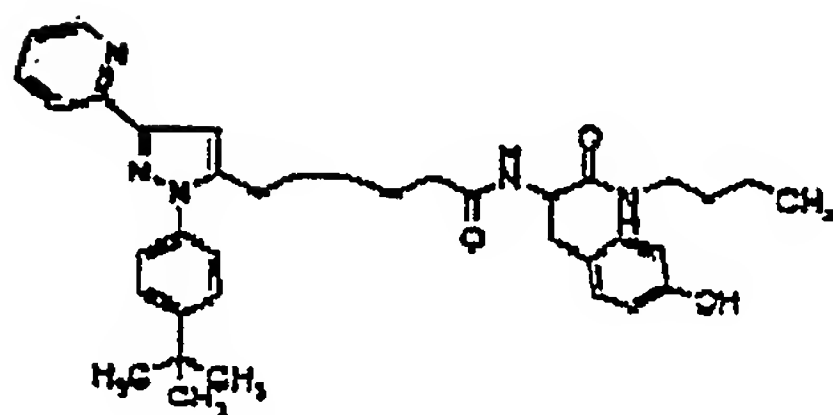
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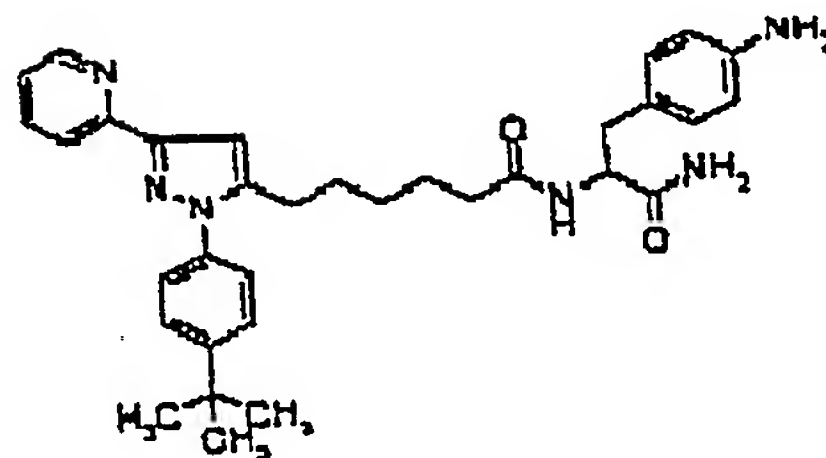
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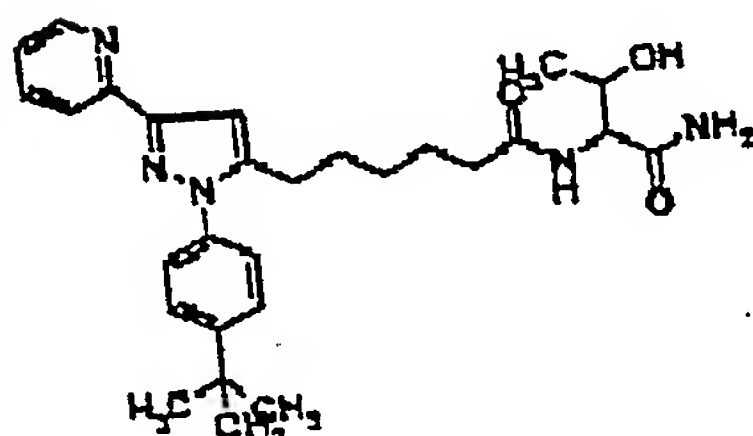
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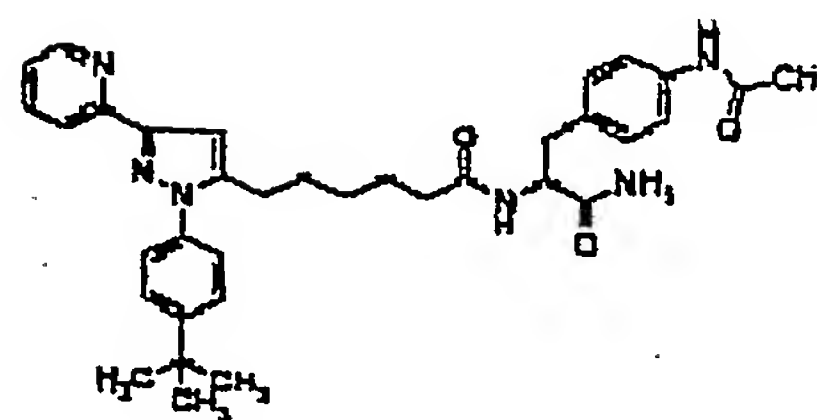
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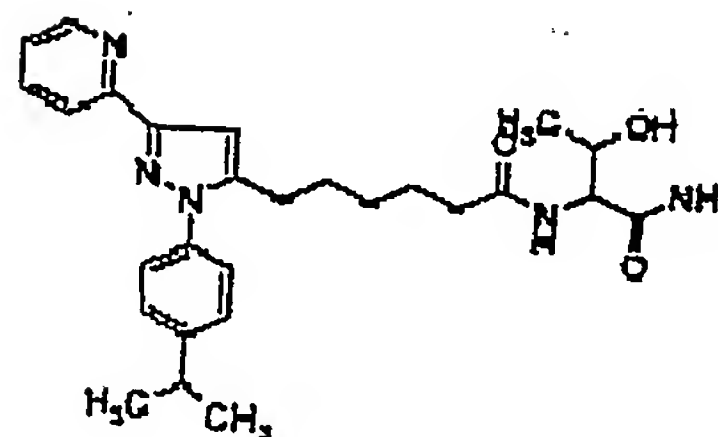
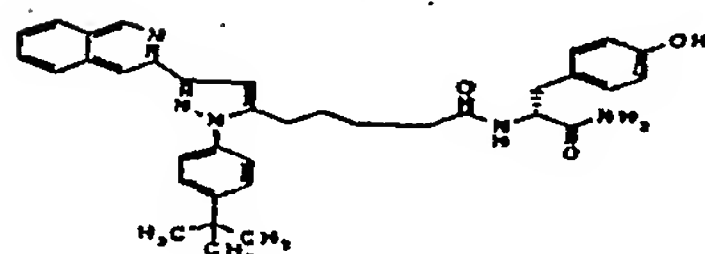
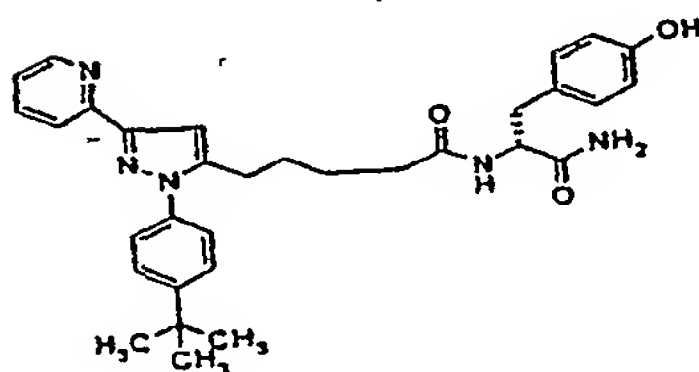
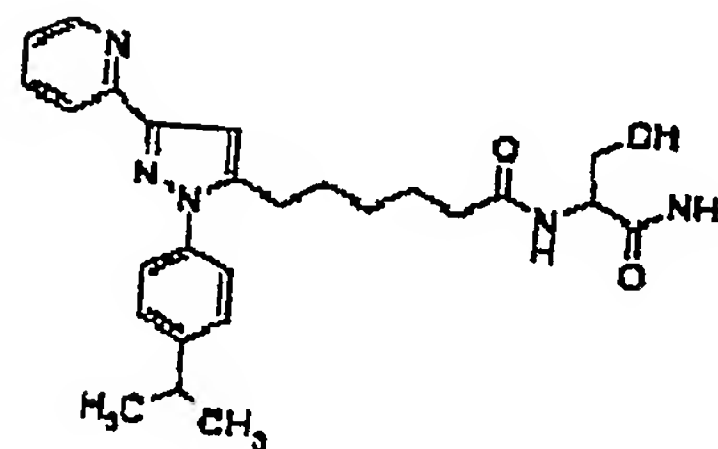
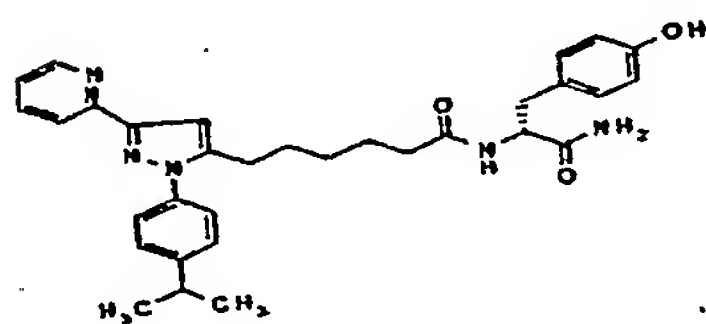
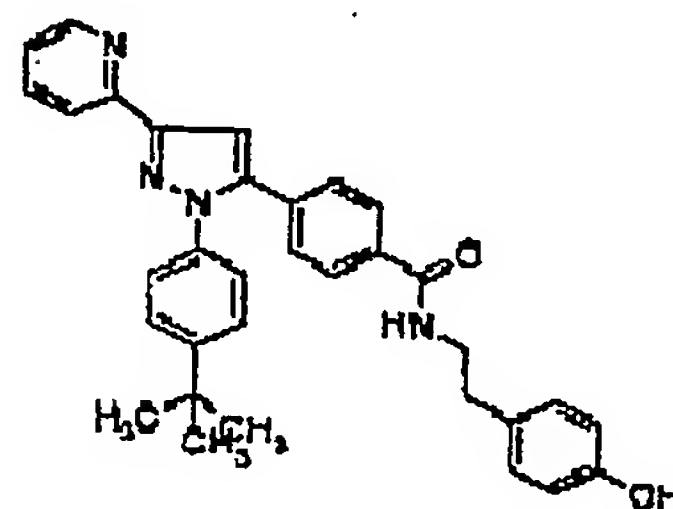
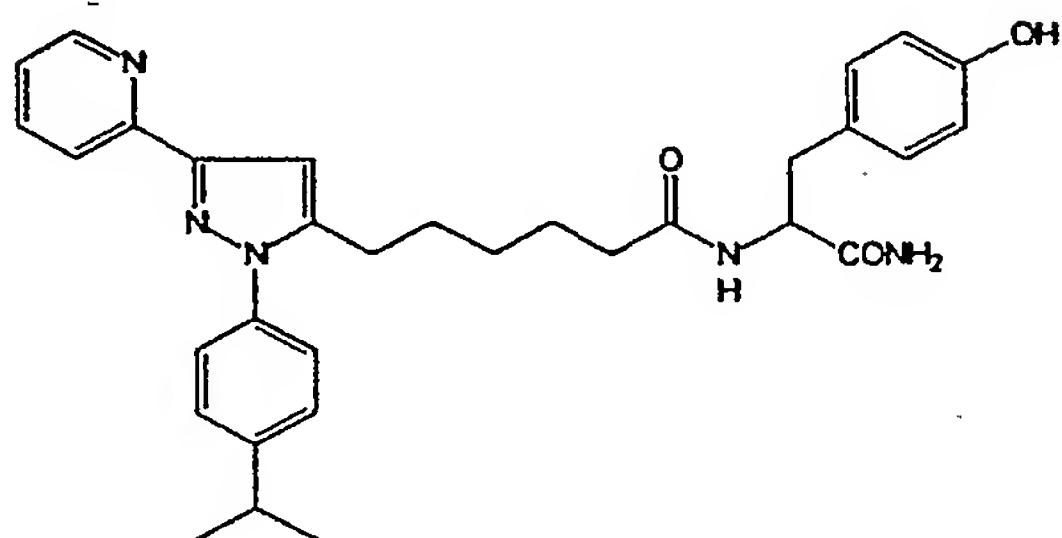
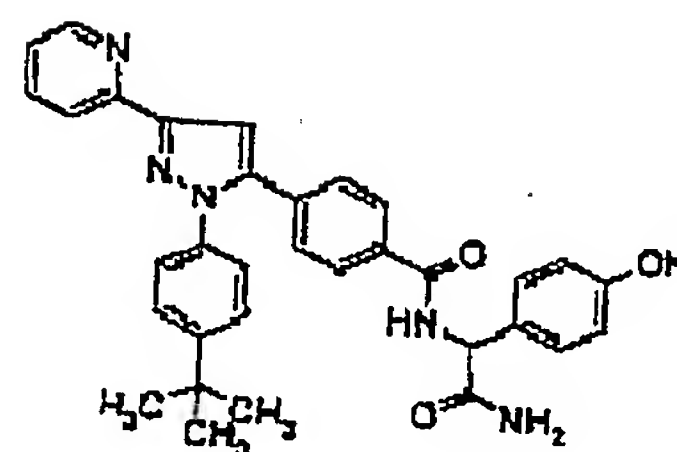
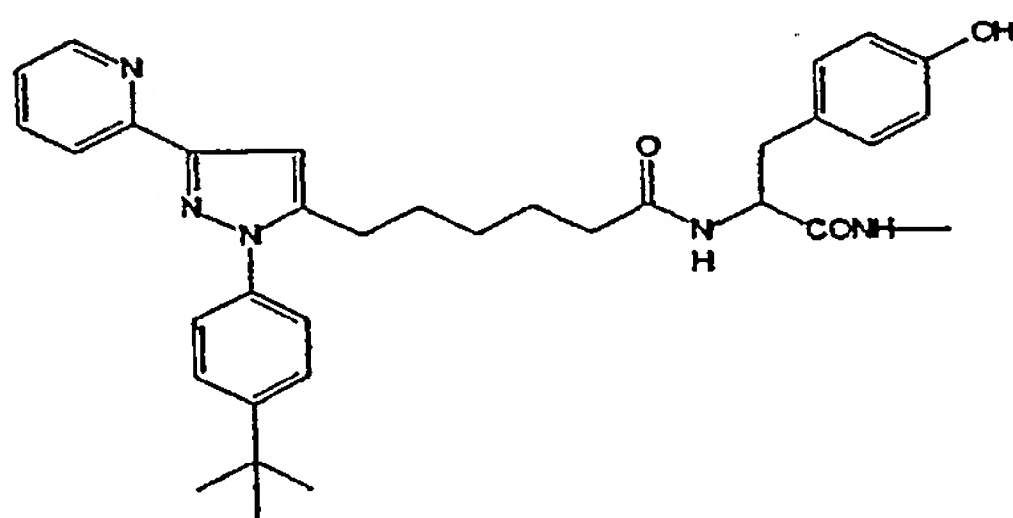
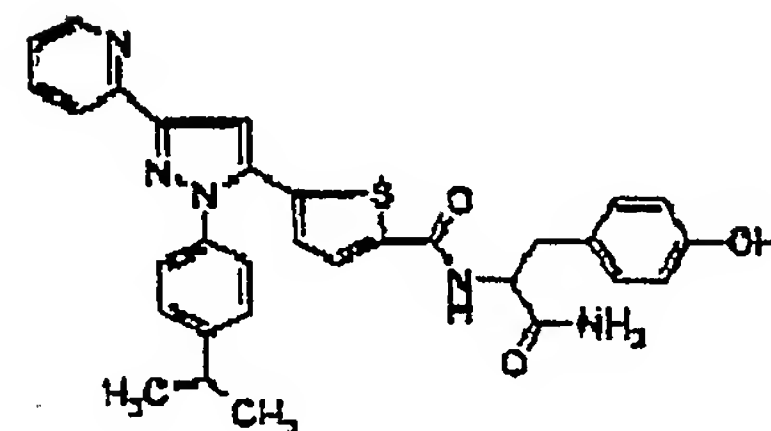
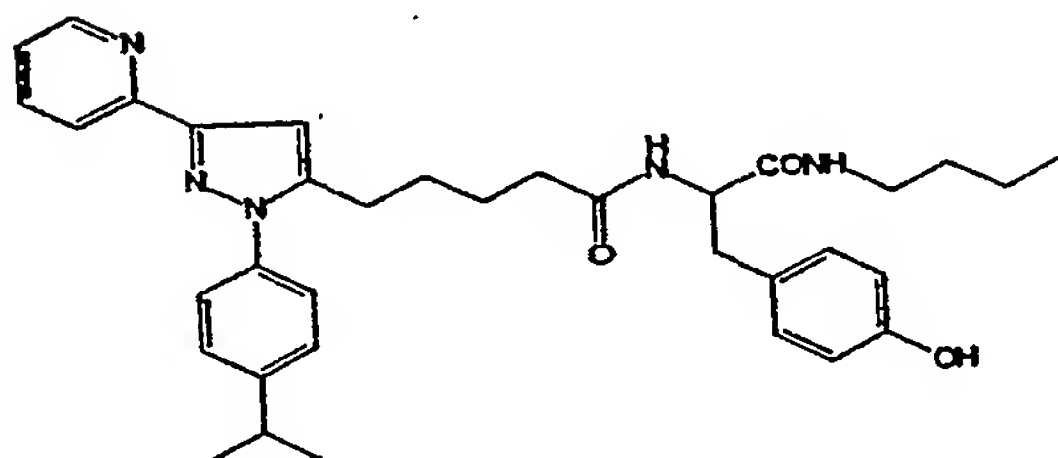
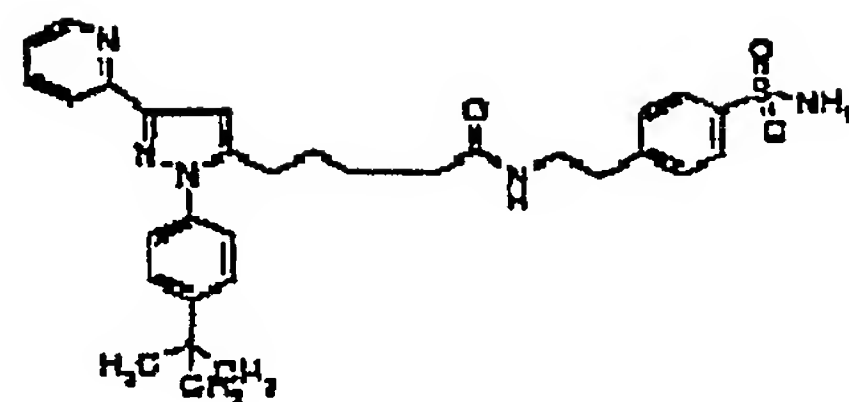
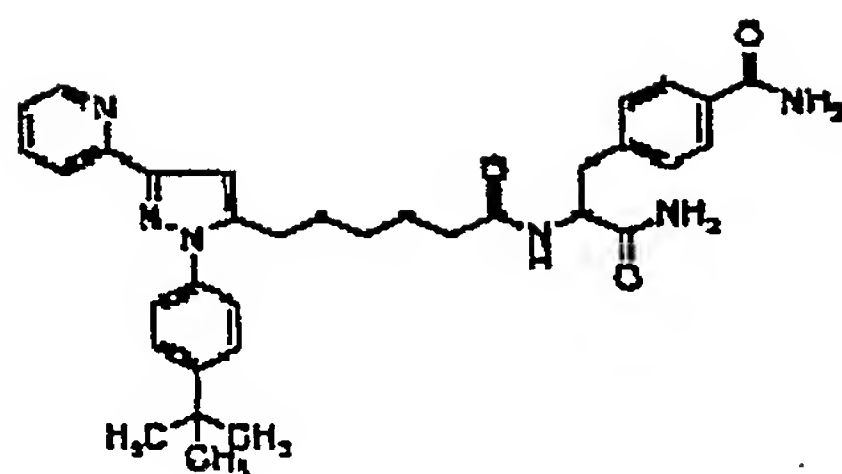
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6.25

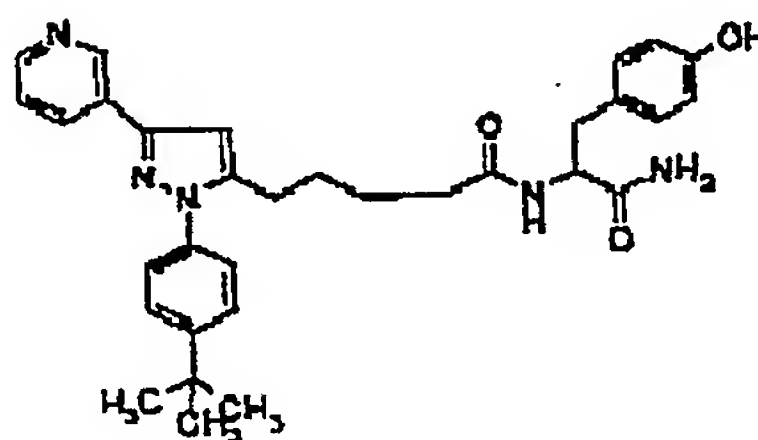


12.5



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A particularly preferred compound of the invention is the following:



Compounds of the invention can be readily prepared. For instance, substituted pyrazoles suitable as starting reagents are commercially available. Generally preferred are pyrazoles having a 3- and/or 5-position non-hydrogen substituent that can be further functionalized to provide a desired compound of the invention. The pyrazole ring can be readily substituted with desired moieties by known ring addition reactions to provide R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> substituents. For instance, non-hydrogen R<sup>2</sup> and R<sup>3</sup> substituents can be provided by Friedel-Crafts-type reactions or Suzuki coupling reactions. See also U.S. Patents 5,986,104; 5,744,493; and 5,486,618, for procedures to prepare substituted pyrazoles.

Suitable pyrazoles for use to prepare compounds of the invention also may be readily synthesized. For example, pyrazole reagents may be synthesized by e.g. reaction of a  $\beta$ -dicarbonyl compound with the corresponding substituted hydrazine or the reaction of the dianion of a methyl hydrazone with the corresponding acid chlorid or acid anhydride. For extensive description of pyrazoles synthesis, see Handbook of Heterocyclic Chemistry, 2<sup>nd</sup> edition, A.R. Katritzky and A.F. Pozharskii, Pergamon, 2000 or Comprehensive Heterocyclic Chemistry III, A.R. Katritzky, C.W. Rees, E.F.V. Scriven, 1<sup>st</sup> Edition, 1996).

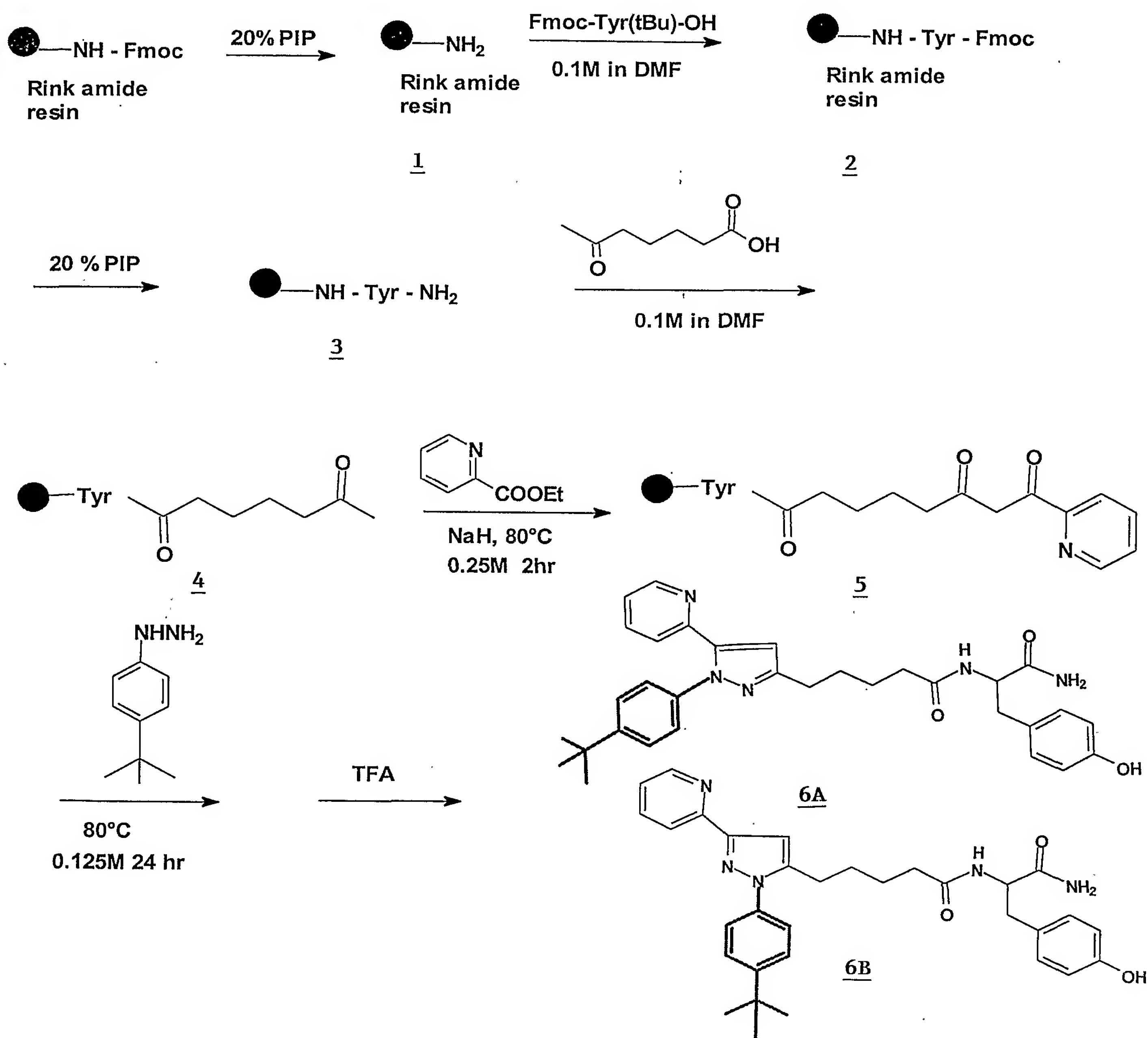
Substituted pyrazole compounds of the invention also may be readily prepared by combinatorial synthetic procedures. For discussions of combinatorial procedures, see, e.g., I. Chaiken et al, *Molecular Diversity and Combinatorial Chemistry*, (ACS, 1996); B. Bunn, *The Combinatorial Index*, (Academic Press 1998). See also A. Marzinzik et al., *Tetrahedron Letters*, 37(7):1003-1006 (1996); Marzinzik et al., *J. Org. Chem.*, 63: 723-727 (1998); and Marzinzik et al: WO 9815532 A1 19980416 for a solid phase combinatorial synthesis of pyrazoles. See also the examples which follow, for exemplary preferred syntheses of pyrazole compounds of the invention.

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More particularly, compounds of the invention including specific regio-  
isomers can be suitably prepared by combinatorial synthetic procedures as outlined in  
the following exemplary Schemes 1, 2 (examples of mixture of isomers) and 3 (as an  
5 example of specific regio isomer). It should be appreciated that the compounds  
shown in the following Schemes are exemplary only, and a variety of other  
compounds can be employed in a similar manner as described below. Additionally,  
while in some instances the Schemes detail certain preferred reaction conditions, it  
will be understood that alternate conditions also may be suitable.

10

Scheme 1

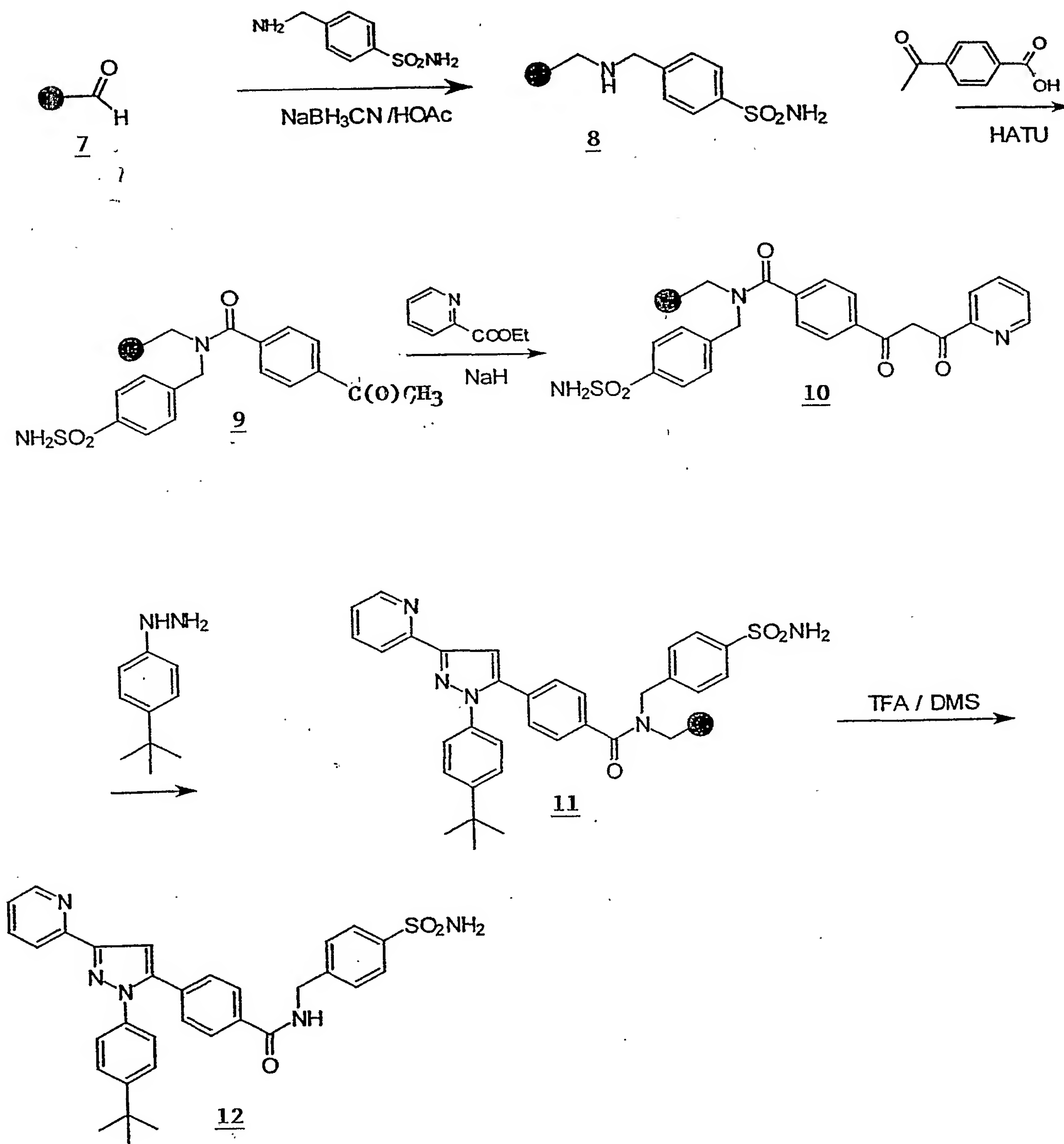




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Thus, as depicted in Scheme 1 above, resin bound amine 1 is reacted with a protected amino acid to provide 2 which is reacted with a keto-acid to provide methyl ketone 4. That methyl ketone is reacted with a substituted ester (provides R<sup>2</sup> substituent of Formula I) in the presence of strong base to yield the di-ketone 5. The adjacent keto groups with interposed methylene react with a hydrazine to provide the substituted pyrazole as regio isomeric mixtures 6A and 6B.

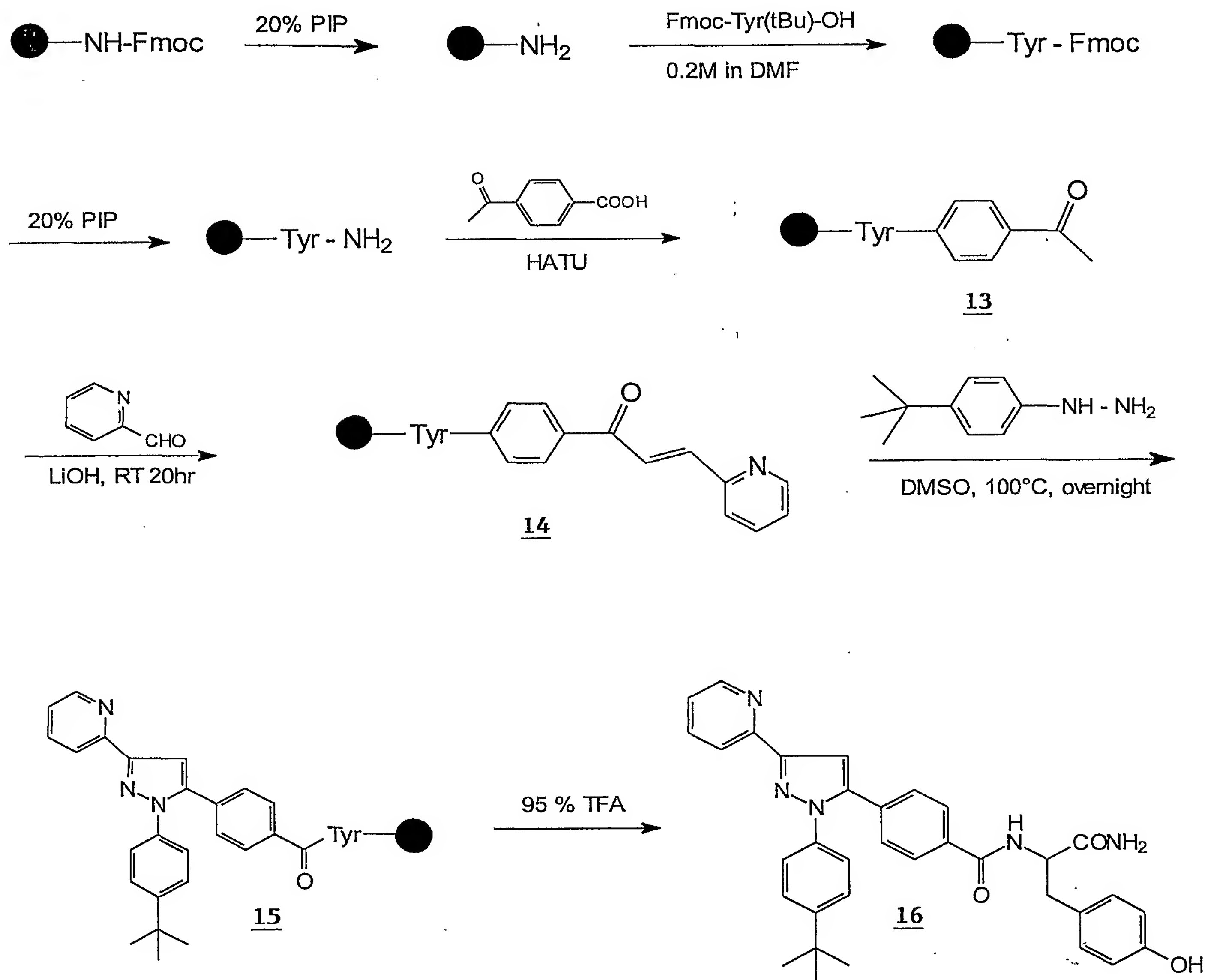
Scheme 2



- 30 -

Scheme 2 above depicts another route for combinatorial synthesis of compounds of the invention. Briefly, resin bound aldehyde 7 is functionalized to give secondary amine 8, which is then reacted with a keto-acid to provide tertiary amine 9 with methyl ketone functionality. Reaction with an ester in the presence of a strong base provide compound 10 having adjacent keto groups with interposed methylene that can be reacted with a hydrazine to provide substituted pyrazole 11 and its isomer. Treatment with strong acid releases the pyrazole 12 from the resin.

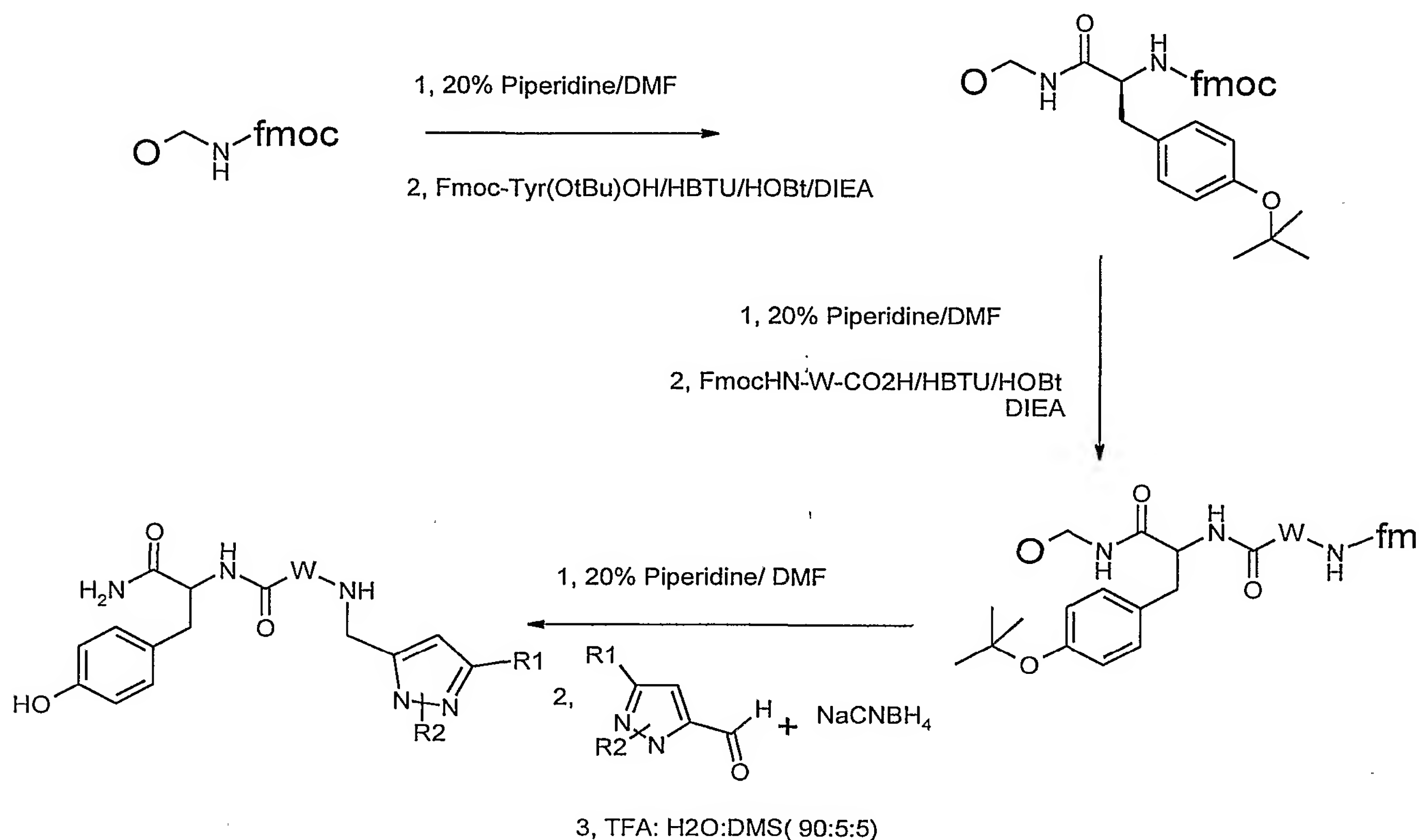
Scheme 3



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Scheme 3 above depicts a selective synthesis of specific regioisomer by combinatorial method. The resin bound methyl ketone 13 on reaction with an appropriate aldehyde in presence of Li(OH) results in  $\alpha,\beta$ -unsaturated ketone 14, which on further reaction with hydrazine results in a specific regio isomer 15, which  
 5 can be released from the resin support in the presence of acid to provide pyrazole 16.

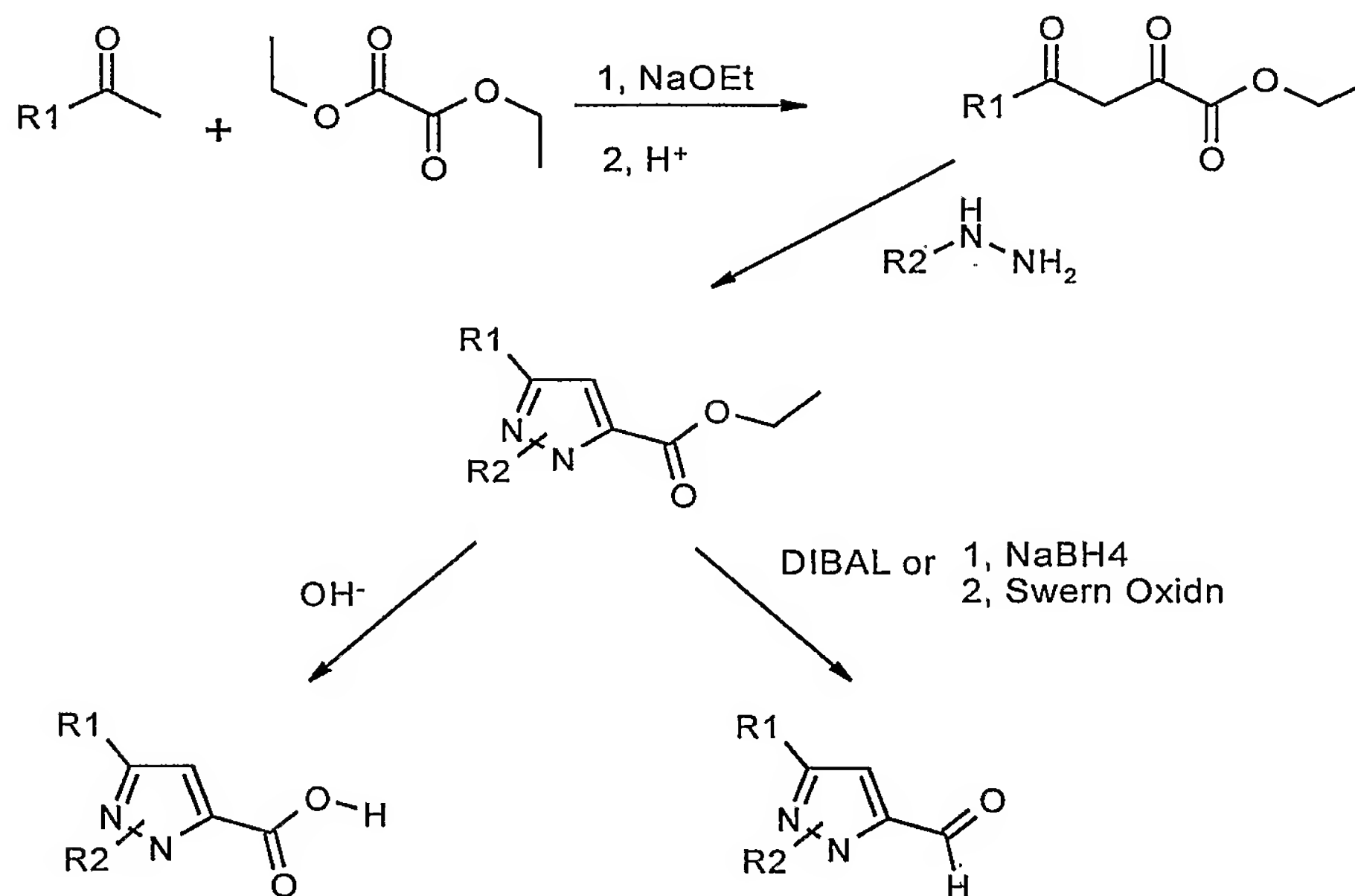
Scheme 4



10 Scheme 4 above depicts the synthesis by combinatorial methods of pyrazole libraries containing a heteroatom on the side chain, particularly compounds of Formulae I, I' and IA where R<sup>1</sup> and R<sup>2</sup> are as defined above for Formulae I, I', and IA, R<sup>3</sup> is H, X is heteroalkylene chain and Y is CO and Z is tyrosine. It should be  
 15 Tyr), by using the appropriate amino acid in the first coupling step other amino acid derivatives may be prepared. In the scheme W is C<sub>1</sub>-C<sub>4</sub> alkyl or 1,3- or 1,4 phenyl radical. All of the reactions shown depict standard coupling reactions which are known to those skilled in the art. The pyrazoles with carboxylic acid or

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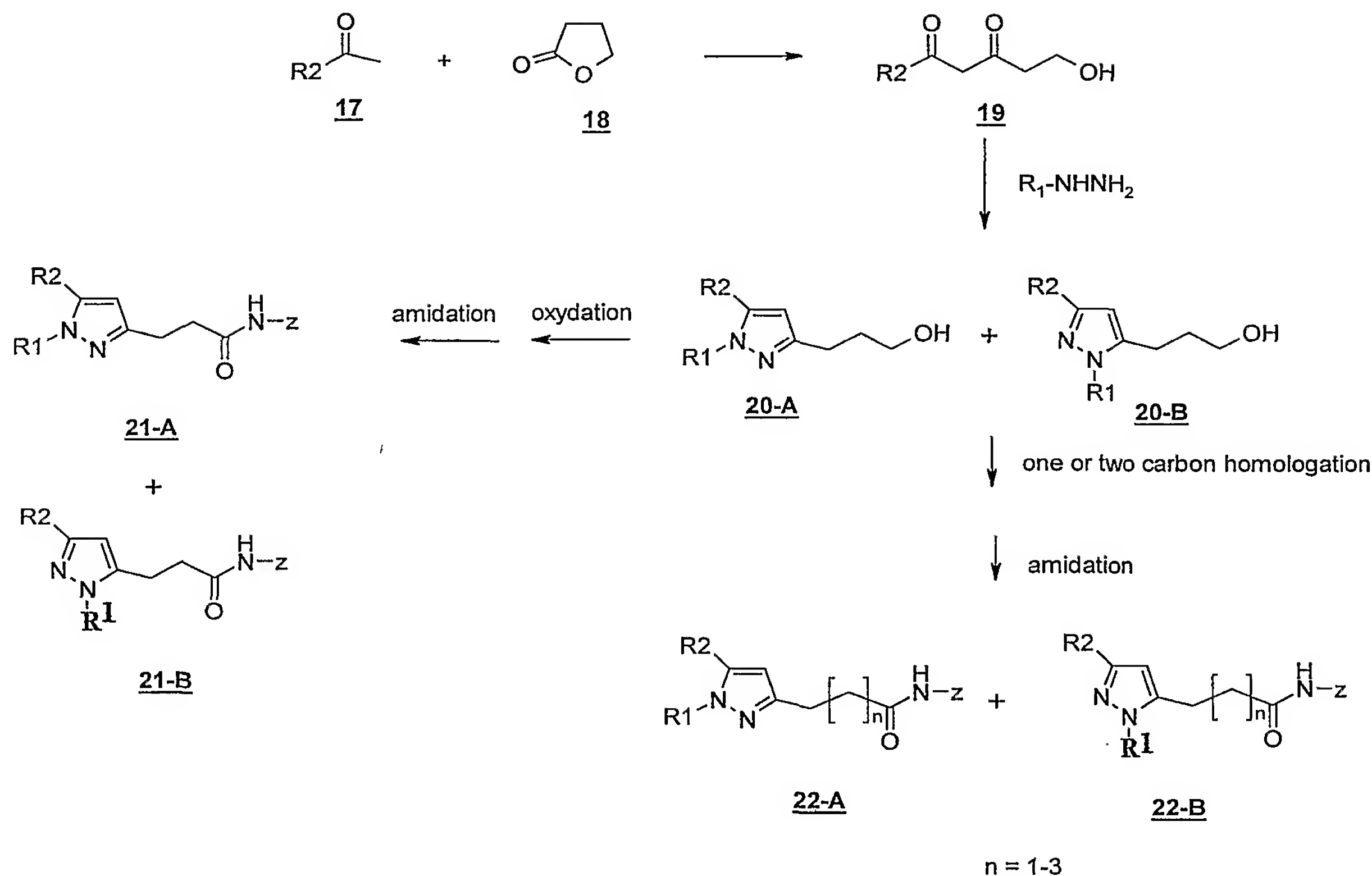
carboxaldehyde in the 3 (or 5) position may be prepared by standard literature procedures as depicted below.



- 5 As already mentioned, compounds of the invention including specific regioisomers can be prepared by solution phase synthetic procedures as outlined in the following exemplary Schemes 5 and 6.

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Scheme 5



Compounds of general formula 20 where  $R^1$  and  $R^2$  have the same definition as in Formula I can be obtained by reaction of β-diketoalcohol 19 with suitable hydrazine as depicted in scheme 5. This procedure is a preferred one as it gives rise to a better regioselectivity in favor of the 20-B pyrazole regioisomer (see W.V. Murray, Tetrahedron Lett., 34, p.1863,1993). The hydroxyalkyl pyrazole thus obtained can be oxidized and reacted with an amine or amino-acid  $Z\text{NH}_2$  where Z is defined as in Formula I using standard amidation conditions (HATU or EDC/HOAT/DIEA for example) to give compounds 21. Homologation by one or two carbons using methods well known to those skilled in the art followed by an amidation step can provide compounds 22.

As an example of such transformation, the hydroxyalkyl derivative 19 can be treated first with iodine in presence of triphenylphosphine and imidazole, then with the anion of *tert*-butyloxyacetate and finally with trifluoroacetic acid to give the corresponding carboxylic acid. Compounds of formula 22 where  $n=3$  can be obtained

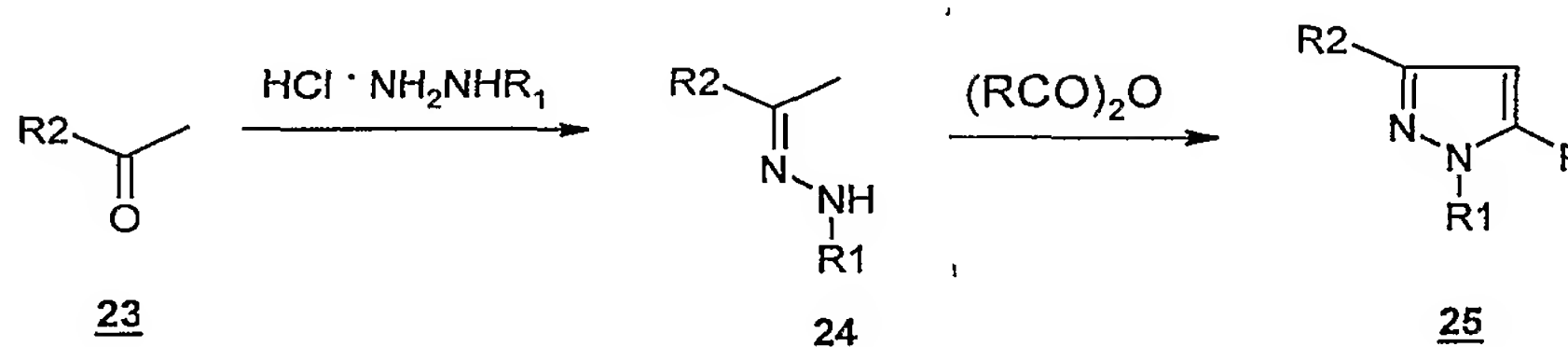


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from such carboxylic acid by coupling with appropriate amine or amino acid  $\text{ZNH}_2$  using standard conditions (as HATU or EDC/HOAT/DIEA).

A second preferred synthetic method for obtaining pyrazoles of the present invention is described in scheme 6. It involves the preparation of hydrazone 24 from an acetyl derivative 23 where  $\text{R}^1$  and  $\text{R}^2$  have the same definition as in Formula I and the appropriate hydrazine. The dianion of the hydrazone is then reacted with an anhydride  $(\text{RCO})_2\text{O}$  to give the pyrazole 25 where R is  $(\text{X})_m-(\text{Y})_n-\text{Z}$  defined as in Formula I or a synthetic precursor which can be easily transformed to  $(\text{X})_m-(\text{Y})_n-\text{Z}$  by methods well known to those skilled in the art. An example of the conditions that can be used for such transformation can be found in S.R. Stauffer, Y. Huang, C.J. Coletta, R. Tedesco, J.A. Katzenellenbogen, *Biorg. Med. Chem.* **2001**, 9, 141 – 150.

Scheme 6

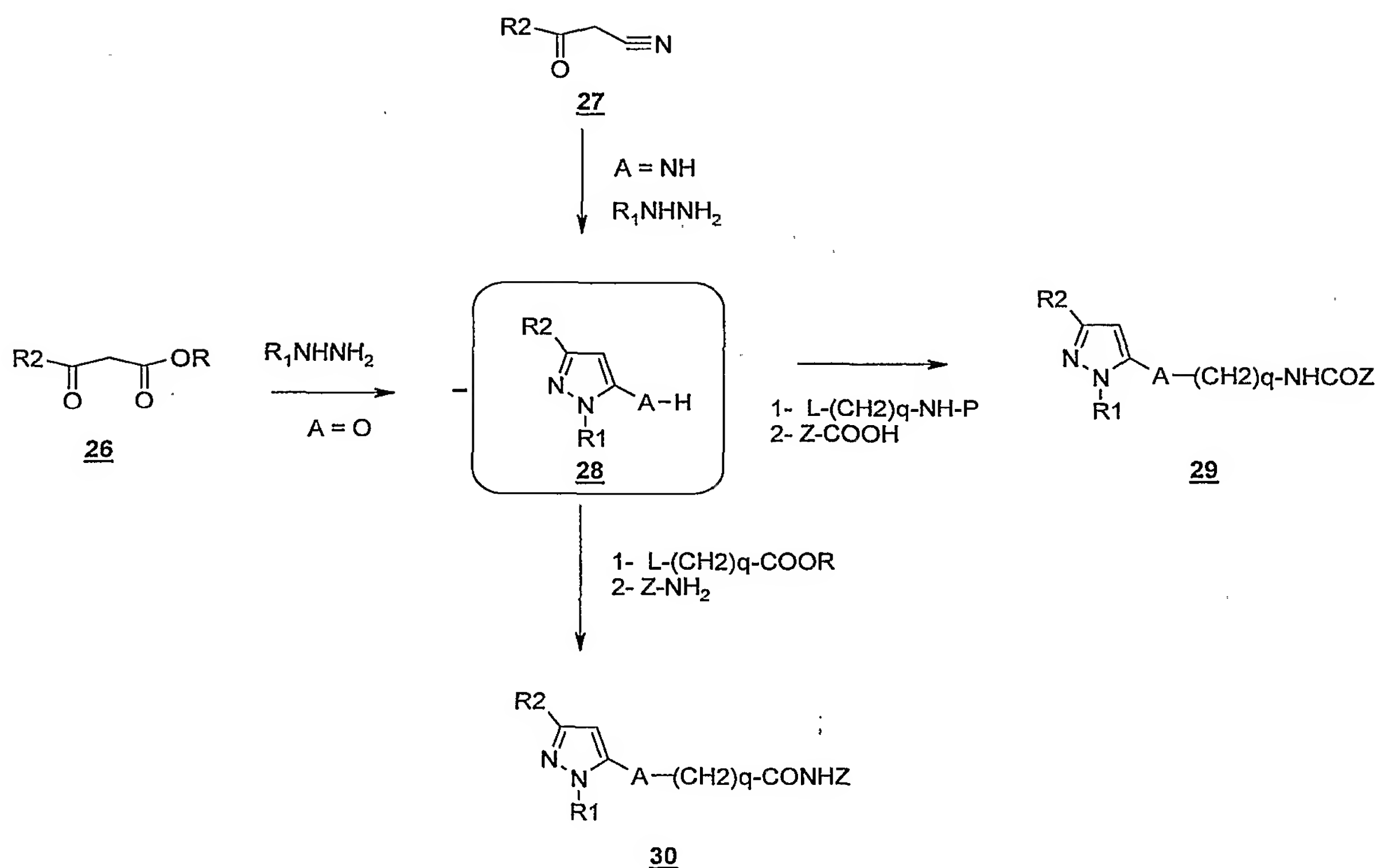


15

In the case of compounds of Formula IC above, suitable methods for preparation include those exemplified in the following Schemes 7 and 8.

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Scheme 7



As showed in Scheme 7 above, compounds of general formula 29 and 30  
 5 wherein  $R^1$ ,  $R^2$  and  $Z$  are defined as in Formula I above,  $A$  is  $O$  or  $NH$  and  $q$  is a  
 number between 1 and 6, may be obtained by alkylation of an intermediate such as 28  
 with a reactant such as  $L-(CH_2)_q-NH-P$  wherein  $L$  is a leaving group (like  $OMs$ ,  
 $OTs$ ,  $Cl$ ,  $Br$  or  $I$ ) and  $P$  an appropriate protecting group. After appropriate  
 protection/deprotection steps, the intermediate thus obtained can be submitted to  
 10 standard amidation conditions well known by those skilled in the art. Depending on  
 the nature of  $A$ , intermediate 28 can be obtained by reaction with suitable hydrazine  
 $R^1NHNH_2$  either from  $\beta$ -ketoester 26 if  $A$  is  $O$  or  $\beta$ -keto-nitrile if  $A$  is  $NH$ . Examples  
 of specific conditions for those reactions can be found in PCT Int.Appl. 9712884 and  
 M.J.Fray, D.J. Bull, M.Kinns, J.Chem.Research (S), p.11 (1992).

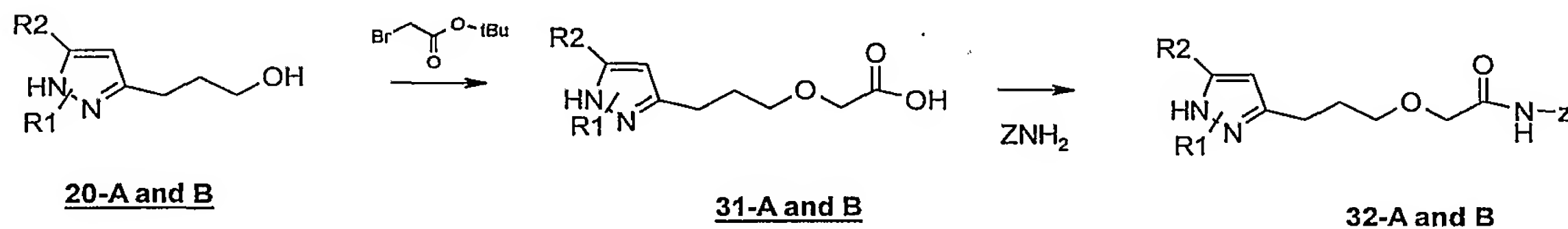
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Some compounds of Formula I-C above can be easily obtained from  
 intermediates 20-A and B (see Scheme 5) using synthetic methods well known by  
 those skilled in the art. Scheme 8 below illustrates one of those possible methods

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yielding to compounds 32-A and B wherein R<sup>1</sup>, R<sup>2</sup> and Z are defined as in Formula I. It should be appreciated that the methods shown in scheme 7 and 8 are exemplary only and that a variety of other methods can be employed to obtain compounds of Formula I-C.

5

Scheme 8

As discussed above, the present invention includes methods for treating infertility in male and female mammals, such as primates, particularly humans. Compounds of the invention will be useful for treatment of infertility conditions currently treated with FSH and/or LH, including female infertility and male spermatogenesis disorders.

The therapeutic methods of the invention generally comprise administration of an effective amount of one or more compounds of the invention to a subject including a mammal, such as a primate, especially a human, in need of such treatment.

Typical candidates for treatment in accordance with the methods of the invention persons suffering from or suspected of suffering from infertility. See the *Merck Manual*, vol. 2, pages 12-17 (16th ed.) for identification of patients suffering from or suspected of infertility, which in the case of humans, can include failure to conceive within one year of unprotected intercourse.

The treatment methods of the invention may be particularly beneficial for female mammals suffering from an ovulatory disorder. Additionally, compounds of the invention can be administered to females undergoing assisted reproductive treatments such as in-vitro fertilization, e.g. to simulate follicular development and maturation. Compounds of the invention also can be administered to males to facilitate adequate spermatogenesis.

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The treatment methods of the invention also will be useful for treatment of infertility in mammals other than humans, such as horses and livestock e.g. cattle, sheep, cows and the like.

5           Compounds of the invention may be administered as a "cocktail" formulation, i.e. coordinated administration of one or more compounds of the invention together with one or more other active therapeutics, particularly one or more other known fertility agents. For instance, one or more compounds of the invention may be administered in coordination with a regime of Follicle Stimulating Hormone and/or  
10   Leutinizing Hormone such as Gonal-F, Metrodin HP or Pergonal.

          The compounds of this invention can be administered by a variety of routes, such as orally or by injection, e.g., intramuscular, intraperitoneal, subcutaneous or intravenous injection, or topically such as transdermally, vaginally and the like.  
15   Compounds of the invention may be suitably administered to a subject in the protonated and water-soluble form, e.g., as a pharmaceutically acceptable salt of an organic or inorganic acid, e.g., hydrochloride, sulfate, hemi-sulfate, phosphate, nitrate, acetate, oxalate, citrate, maleate, mesylate, etc.

20           Compounds of the invention can be employed, either alone or in combination with one or more other therapeutic agents as discussed above, as a pharmaceutical composition in mixture with conventional excipient, i.e., pharmaceutically acceptable organic or inorganic carrier substances suitable for oral, parenteral, enteral or topical application which do not deleteriously react with the active compounds and are not  
25   deleterious to the recipient thereof. Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions, alcohol, vegetable oils, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, petroethral fatty acid esters, hydroxymethyl-cellulose, polyvinylpyrrolidone, etc. The  
30   pharmaceutical preparations can be sterilized and if desired mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, colorings, flavorings and/or aromatic substances and the like which do not deleteriously react with the active compounds.

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For oral administration, pharmaceutical compositions containing one or more substituted pyrazole compounds of the invention may be formulated as e.g. tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups, elixers and the like. Typically suitable are tablets, dragees or capsules having talc and/or carbohydrate carrier binder or the like, the carrier preferably being lactose and/or corn starch and/or potato starch. A syrup, elixir or the like can be used wherein a sweetened vehicle is employed. Sustained release compositions can be formulated including those wherein the active component is protected with differentially degradable coatings, e.g., by microencapsulation, multiple coatings, etc.

For parenteral application, e.g., sub-cutaneous, intraperitoneal or intramuscular, particularly suitable are solutions, preferably oily or aqueous solutions as well as suspensions, emulsions, or implants, including suppositories. Ampules are convenient unit dosages.

For topical applications, formulations may be prepared in a topical ointment or cream containing one or more compounds of the invention. When formulated as an ointment, one or more compounds of the invention suitably may be employed with either a paraffinic or a water-miscible base. The one or more compounds also may be formulated with an oil-in-water cream base. Other suitable topical formulations include e.g. lozenges and dermal patches.

It will be appreciated that the actual preferred amounts of active compounds used in a given therapy will vary according to the specific compound being utilized, the particular compositions formulated, the mode of application, the particular site of administration, etc. Optimal administration rates for a given protocol of administration can be readily ascertained by those skilled in the art using conventional dosage determination tests conducted with regard to the foregoing guidelines. See also Remington's Pharmaceutical Sciences. In general, a suitable effective dose of one or more compounds of the invention, particularly when using the more potent compound(s) of the invention, will be in the range of from 0.01 to 100 milligrams per



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kilogram of bodyweight of recipient per day, preferably in the range of from 0.01 to 20 milligrams per kilogram bodyweight of recipient per day, more preferably in the range of 0.05 to 4 milligrams per kilogram bodyweight of recipient per day. The desired dose is suitably administered once daily, or several sub-doses, e.g. 2 to 4 sub-

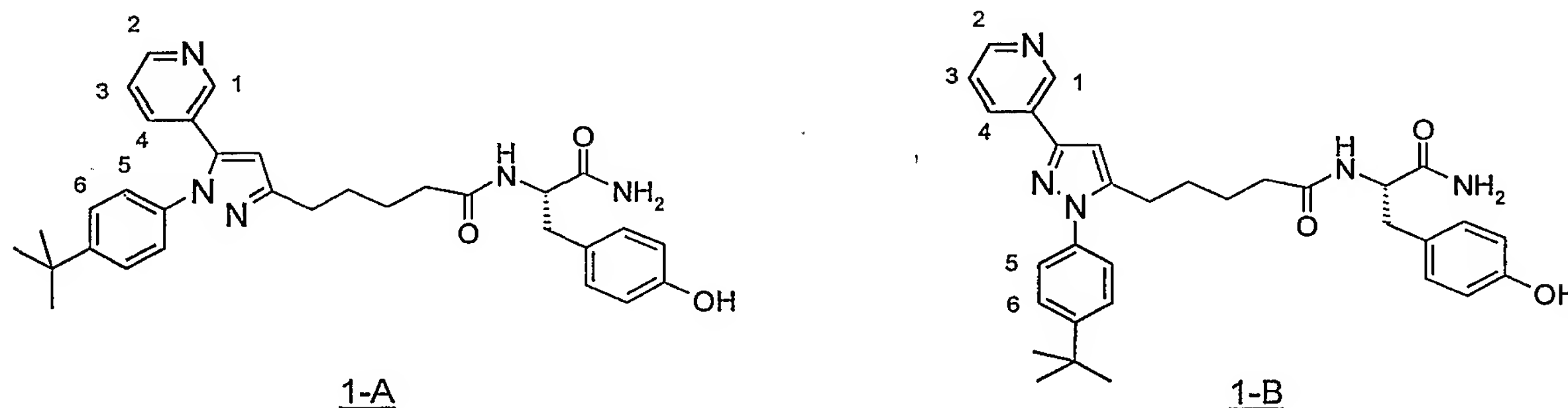
5 doses, are administered at appropriate intervals through the day, or other appropriate schedule. Such sub-doses may be administered as unit dosage forms, e.g., containing from 0.05 to 10 milligrams of compound(s) of the invention, per unit dosage.

The entire text of all documents cited herein are incorporated by reference

10 herein. The following non-limiting examples are illustrative of the invention.

Example 1: Synthesis of N-(5-[1-(4-*tert*-butylphenyl)-5-pyridin-3-yl-1H-pyrazol-3-yl]pentanoyl)tyrosinamide (1-A) and N-(5-[1-(4-*tert*-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]pentanoyl)tyrosinamide (1-B) on solid phase

15



Rink-amide resin (30g, loading = 0.65mmol/g) was shaken in a large peptide

20 vessel in a 20% piperidine solution in DMF (200mL) for 30 min. This operation was repeated 2 times. The resin was then washed with DMF (3x), NMP (2x), MeOH (2x) and DCM (2x) and dried under vacuum for 30 min. The deprotected resin was transferred into a 1 L bottle and shaken for 27h in a solution containing Fmoc-

25 Tyr(*t*Bu)-OH (90g), HATU (74g) and DIEA (60mL) in 360 mL of DMF. After this time, the resin was transferred into a peptide vessel, washed with DMF (3x), DCM (2x), MeOH (2x), DMF (1x), DCM (1x) and dried under vacuum for 15 min. It was then shaken in a 20% piperidine solution in DMF (200mL) for 30 min 3 times, washed with DMF (3x), NMP (2x), MeOH (2x), DCM (2x) and dried under vacuum

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for 15 min. For the next step, the resin was transferred again into a 1 L bottle and shaken for 48h in a solution of acetylvaleric acid (28.1g), HATU (74.1g) and DIEA (66mL) in DMF (360 mL). Same washing procedure as for the preceding coupling step was followed. The resin was dried under vacuum and divided into two portions of  
5 about 32g (portion 1) and 31g (portion 2).

Portion 1 was transferred into a 1L bottle flushed with nitrogen containing a solution of methylnicotinate (40g) in 200mL of DMA. Sodium hydride 95% (70g) was then added in small portions into the mixture with constant nitrogen flushing.  
10 The bottle was placed in an ice bath and agitated by hand until the hydrogen release had stopped. It was then heated at 85°C for 2 hours with occasional hand agitation. After that time, the mixture was chilled to room temperature and poured slowly into a beaker containing ice and a solution of 15% acetic acid in water. Transfer into a peptide vessel was operated before the standard washing and drying steps. The 18g of  
15 resin thus obtained were poured into a 1L bottle containing 4-tert-butylphenylhydrazine hydrochloride (39.1g) and DIEA (33.1 mL) in DMA (360 mL) and heated for 24 hours at 80°C. The bottle was chilled to room temperature and the resin was washed and dried following standard procedure. Finally, it was cleaved with 100mL of DCM/TFA (2:1) and the residue was concentrated under reduced  
20 pressure. It was dissolve in ethyl acetate and washed with slightly basic solution (pH ~8.5-9 obtained with diluted NH<sub>4</sub>OH). The organic layer was dried over magnesium sulfate, filtered and concentrated to give 3.65g of crude (yield ~70%). This crude contained a mixture of the two possible pyrazole regioisomers 1A and 1B with a ratio of about 9:1. The two regioisomers were separated by reversed phase HPLC using  
25 DELTAPAK C<sub>18</sub> column with a linear gradient of 0.1% TFA water/acetonitrile 95:5 to 60:40 in one hour.

Structures were assigned by Nuclear Overhauser experiments performed on a JEOL 400 MHz NMR apparatus. There were NOE cross peaks displayed between the  
30 proton 5 and proton 1 and 4 for isomer A, indicating that the phenyl ring is close from the pyridine ring and no NOE effect observed between those protons for isomer B.

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Isomer 1-A (more polar): trifluoroacetate salt of N-(5-[1-(4-*tert*-butylphenyl)-5-pyridin-3-yl-1H-pyrazol-3-yl]pentanoyl)tyrosinamide

<sup>1</sup>H NMR (DMSO) : 1.28 (s, 9H), 1.55 (m, 4H), 2.12 (t, J = 7.3Hz, 2H), 2.63 (m, 3H),  
5 2.86 (dd, J = 5.3 and 13.9 Hz, 1H), 4.35 (m, 1H), 5.60 (brs, 1H), 6.61 (s, 1H), 6.62 (d, J = 8.8 Hz, 2H), 6.98 (m, 1H), 7.01 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 8.8 Hz, 2H),  
7.36 (m, 1H), 7.42 (d, J = 8.8 Hz, 2H), 7.51 (dd, J = 8.1 and 5.1 Hz, 1H), 7.75 (dt, J =  
8.1 and 2.2 Hz, 1H), 8.52 (dd, J = 2.2 and 0.73 Hz, 1H), 8.58 (dd, J = 4.9 and 1.5 Hz,  
1H).

10

MS (ESI, pos.) : 540 (M+1)

Isomer 1-B (less polar) : trifluoroacetate salt of N-(5-[1-(4-*tert*-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]pentanoyl)tyrosinamide

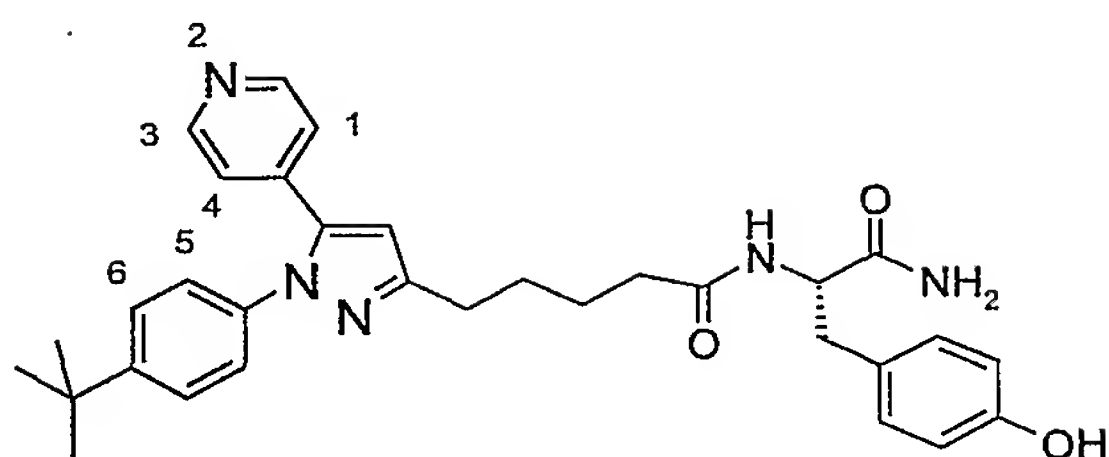
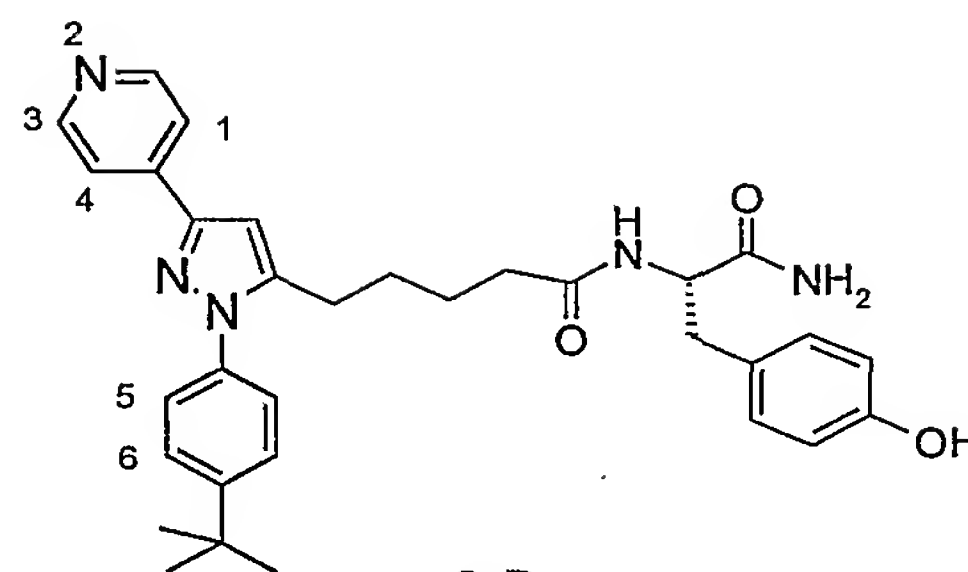
15

<sup>1</sup>H NMR (DMSO): 1.34 (s, 9H), 1.47 (m, 4H), 2.05 (t, J = 9.1 Hz, 2H), 2.61 (m, 1H),  
2.64 (t, J = 6.9 Hz, 2H), 2.84 (m, 1H), 4.34 (m, 1H), 6.30 (brs, 1H), 6.59 (d, J = 8.4  
Hz, 2H), 6.98 (m, 1H), 6.99 (d, J = 8.4 Hz, 2H), 7.02 (s, 1H), 7.37 (m, 1H), 7.48 (d, J  
= 8.8 Hz, 2H), 7.58 (d, J = 8.8 Hz, 2H), 7.86 (d, J = 8.4 Hz, 1H), 7.92 (dd, J = 8.1 and  
20 5.5 Hz, 1H), 8.72 (dt, J = 8.4 and 1.46 Hz, 1H), 8.76 (dd, J = 5.49 and 1.46 Hz, 1H),  
9.24 (d, J = 2.2 Hz, 1H).

MS (ESI, pos.) : 540 (M+1)

25 Example 2 : Synthesis of N-(5-[1-(4-*tert*-butylphenyl)-5-pyridin-4-yl-1H-pyrazol-3-yl]pentanoyl)tyrosinamide (2-A) and N-(5-[1-(4-*tert*-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]pentanoyl)tyrosinamide (2-B)

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2-A2-B

Those compounds were synthesized from the portion 2 (31g) of resin obtained in Example 1 above following exactly the same procedure. All the reagents and quantities are the same except that methylnicotinate was replaced by

5 methylisonicotinate.

2.5g of crude were obtained (48% yield) and contained a mixture of the two possible pyrazole regioisomers 2A and 2B with a ratio of about 9:1. The two regioisomers were separated using the same conditions as those described in example 1. The

10 structures were assigned by analogy with compounds 1A and 1B.

Isomer 2-A (more polar): trifluoroacetate salt of N-(5-[1-(4-*tert*-butylphenyl)-5-pyridin-4-yl-1H-pyrazol-3-yl]pentanoyl)tyrosinamide

15 <sup>1</sup>H NMR (DMSO) : 1.29 (s, 9H), 1.52 (m, 4H), 2.10 (t, J = 7.3Hz, 2H), 2.55 (m, 3H), 2.83 (dd, J = 4.4 and 14.3 Hz, 1H), 4.35 (m, 1H), 6.61 (d, J = 6.6 Hz, 2H), 6.77 (s, 1H), 7.00 (s, 1H), 7.01 (d, J = 6.9 Hz, 2H), 7.22 (d, J = 6.6 Hz, 2H), 7.38 (m, 3H), 7.45 (d, J = 6.9 Hz, 2H), 7.88 (d, J = 8.4 Hz, 1H), 8.63 (d, J = 4.8 Hz, 2H), 9.2 (brs, 1H).

20

MS (ESI, pos.) : 540 (M+1)

Isomer 2-B (less polar) : trifluoroacetate salt of N-(5-[1-(4-*tert*-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]pentanoyl)tyrosinamide

25

<sup>1</sup>H NMR (DMSO) : 1.34 (s, 9H), 1.43 (m, 4H), 2.04 (t, J = 9.1 Hz, 2H), 2.50 (m, 1H), 2.64 (m, 2H), 2.83 (dd, J = 3.3 and 9.2 Hz, 1H), 4.35 (m, 1H), 6.58 (d, J = 6.9 Hz, 2H), 6.98 (m, 3H), 7.14 (s, 1H), 7.38 (s, 1H), 7.49 (d, J = 6.9 Hz, 2H), 7.59 (d, J = 6.9

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Hz, 2H), 7.86 (d, J = 8.4 Hz, 1H), 8.17 (d, J = 4.7 Hz, 2H), 8.78 (d, J = 4.1 Hz, 2H), 9.2 (brs, , 1H).

MS (ESI, pos.) : 540 (M+1)

5

Elemental analysis:  $C_{32}H_{37}N_5O_3 \cdot TFA \cdot 1.5H_2O$ , theoretical : C, 59.99%; H, 6.07%; N, 10.29% ; experimental : C, 60.12%; H, 5.95%; N, 10.27%.

Example 3: Combinatorial synthesis of pyrazole library of the invention.

10

A library of ~2500 pyrazoles synthesized via Fmoc/t-Butyl chemistry using either IRORI AccuTag / Robin technology. 20 microkans each in three glass bottles containing Fmoc Rink Amide MBHA resin (25mg, 0.59 mmol/g) were treated with 20% piperidine/DMF (30mL, 3 x 30min) and then rinsed with DMF and acylated with 0.1 M solution of Fmoc amino acid (3 mmol) in DMF (30mL), HATU (3 mmol) and DIEA (6 mmol) at room temperature for 16 hours, rinsed with DMF. Fmoc was removed with 20% piperidine/DMF (100mL, 3 x 30min), rinsed with DMF. 30 microkans in two glass bottles resin were acylated with 0.1 M solution of acetyl carboxylic acid (4.5mmol) in DMF (45mL), HATU (4.5 mmol) and DIEA (9 mmol) at room temperature for 16 hours and then rinsed with DMF. Claisen condensation was carried out with 30 microkans in two glass bottles with 0.25 M solution of ester (11.25mmol), 95% NaH (11.25mmol) in DMA at 90°C in the oven for 2 hours. The microkans were washed (DMA, MeOH, DMF and  $CH_2Cl_2$ ) and dried under reduced pressure. Cyclization was carried out with 12 microkans in 5 glass bottles with 0.125M solution of hydrazine (2.25mmol), DIEA (2.25mmol) in DMA (18 mL) at 80°C in the oven for 24 hours, rinsed and dried under reduced pressure. The final cleavage of resin was carried out with TFA at 2 hours in the IRORI cleavage block. The residue was then co-evaporated with  $CH_3CN$  under reduced pressure.

All of the crude pyrazoles were analyzed by reversed phase HPLC using DELTAPAK  $C_{18}$ , 5 $\mu$ M column, eluted with a linear gradient of 0.1% TFA in  $CH_3CN$ /water (0%  $CH_3CN$ /100% water) to 0.1% TFA in  $CH_3CN$ /water (100%  $CH_3CN$ /0% water) over a 30 minute period with flow rate of 1.5mL/minute. The purity of the samples were determined and were essentially found to contain the

30



pyrazole in 60% purity as a mixture of regioisomers. The mass were confirmed by matrix-assisted laser desorption ionization time of flight mass spectral analysis (MALDI-TOF, PE Biosystem, Inc.). Generally the pyrazoles gave the mass of MH<sup>+</sup> or M+Na<sup>+</sup> or within experimental error of the calculated value.

5

Example 4: Compound purification.

The crude pyrazoles prepared in Example 3 above were purified by reversed phase HPLC using DELTAPAK C<sub>18</sub>, 5μM column, eluted with a linear gradient of 0.1% TFA in CH<sub>3</sub>CN/water (0% CH<sub>3</sub>CN/100% water) to 0.1% TFA in CH<sub>3</sub>CN/water (100% CH<sub>3</sub>CN/0% water) over a 30 minute period with flow rate of 15mL/minute. The purity of the samples were determined and were essentially found to contain one component. The mass were confirmed by matrix-assisted laser desorption ionization time of flight mass spectral analysis (MALDI-TOF, PE Biosystem, Inc.). Generally the pyrazoles gave the mass of MH<sup>+</sup> or M+Na<sup>+</sup> or within experimental error of the calculated value.

15

For example, the following compounds were prepared by this procedure:

- N-{5-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]pentanoyl}tyrosinamide, [M +H] = 540;
- 20 N-{5-[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]pentanoyl}tyrosinamide, [M +H] = 540;
- N-{5-[1-(4-tert-butylphenyl)-5-pyridin-3-yl-1H-pyrazol-3-yl]pentanoyl}tyrosinamide, [M +H] = 540;
- N-{5-[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]pentanoyl}tyrosinamide, [M +H] = 540;
- 25 N-{5-[1-(4-tert-butylphenyl)-5-pyridin-4-yl-1H-pyrazol-3-yl]pentanoyl}tyrosinamide, [M +H] = 540;
- N-{5-[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]pentanoyl}-N,N-dimethyltyrosinamide, [M +H] = 554;
- 30 N-[4-(1-butyl-3-isoquinolin-3-yl-1H-pyrazol-5-yl)benzoyl]tyrosinamide, [M +H] = 534;
- N-{5-[1-(4-isopropylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]pentanoyl}tyrosinamide, [M +H] = 526;

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- N-{6-[1-(4-isopropylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}tyrosinamide,  
[M +H] = 540;
- N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}-3-  
hydroxyphenylalaninamide, [M +H] = 554;
- 5 N-[1-(aminocarbonyl)-3-(4-hydroxyphenyl)propyl]-5-[1-(4-tert-butylphenyl)-3-  
pyridin-2-yl-1H-pyrazol-5-yl]pentanamide, [M +H] = 554;
- N-[5-(1-butyl-3-isoquinolin-3-yl-1H-pyrazol-5-yl)pentanoyl]tyrosinamide, [M +H] =  
514;
- N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}serinamide,  
10 [M +H] = 478;
- N-{6-[1-(4-iso-propylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}serinamide,  
[M +H] = 464;
- N-{6-[1-(4-iso-propylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}threonamide,  
[M +H] = 478;
- 15 N-{5-[1-(4-isopropylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]pentanoyl}tyrosinamide,  
[M +H] = 526;
- 6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]-N-[2-(4-  
hydroxyphenyl)ethyl]hexanamide, [M +H] = 511;
- N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}tyrosinamide,  
20 [M +H] = 554;
- N-{5-[1-(4-tert-butylphenyl)-3-isoquinolin-3-yl-1H-pyrazol-5-  
yl]pentanoyl}tyrosinamide, [M +H] = 590;
- N-{6-[1-(4-tert-butylphenyl)-3-isoquinolin-3-yl-1H-pyrazol-5-  
yl]hexanoyl}tyrosinamide, [M +H] = 604;
- 25 N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}-N-  
methyltyrosinamide, [M +H] = 568;
- N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}-4-  
(hydroxymethyl)phenylalaninamide, [M +H] = 568;
- 4-amino-N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-  
30 yl]hexanoyl}phenylalaninamide, [M +H] = 553;
- 4-(acetylamino)-N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-  
yl]hexanoyl}phenylalaninamide, [M +H] = 595;
- 4-(aminocarbonyl)-N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-

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- yl]hexanoyl}phenylalaninamide,  $[M + H] = 581$ ;
- N-butyl-N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}tyrosinamide,  $[M + H] = 610$ ;
- N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}threonamide,
- 5  $[M + H] = 492$ ;
- N-[2-amino-1-(4-hydroxyphenyl)-2-oxoethyl]-6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanamide,  $[M + H] = 540$ ;
- N-{2-[4-(aminosulfonyl)phenyl]ethyl}-5-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]pentanamide,  $[M + H] = 560$ ;
- 10 N-({5-[1-(4-isopropylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]thien-2-yl}carbonyl)tyrosinamide,  $[M + H] = 552$ ;
- N-[2-amino-1-(4-hydroxyphenyl)-2-oxoethyl]-4-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]benzamide,  $[M + H] = 546$ ;
- 4-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]-N-[2-(4-
- 15 hydroxyphenyl)ethyl]benzamide,  $[M + H] = 517$ ;
- N-{3-[1-(4-tert-butylbenzyl)-3-isoquinolin-3-yl-1H-pyrazol-5-yl]benzoyl}tyrosinamide,  $[M + H] = 608$ ;
- N-{5-[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]pentanoyl}tyrosinamide,  $[M + H] = 540$ ;
- 20 N-{3-[1-(4-tert-butylbenzyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]benzoyl}tyrosinamide,  $[M + H] = 574$ ;
- N-{3-[1-(4-tert-butylphenyl)-3-isoquinolin-3-yl-1H-pyrazol-5-yl]benzoyl}tyrosinamide,  $[M + H] = 610$ ;
- N-[4-(1-butyl-3-isoquinolin-3-yl-1H-pyrazol-5-yl)benzoyl]tyrosinamide,  $[M + H] =$
- 25 534;
- N-{3-[1-(4-tert-butylbenzyl)-3-quinolin-3-yl-1H-pyrazol-5-yl]benzoyl}tyrosinamide,  $[M + H] = 624$ ;
- N-{3-[3-isoquinolin-3-yl-1-(4-propylphenyl)-1H-pyrazol-5-yl]benzoyl}tyrosinamide,  $[M + H] = 610$ ;
- 30 N-{3-[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]benzoyl}tyrosinamide,  $[M + H] = 560$ ;
- N-{4-[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]benzoyl}tyrosinamide,  $[M + H] = 560$ ;

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- N-{5-[1-(4-tert-butylbenzyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]pentanoyl}tyrosinamide,  
[M + H] = 554;
- N-{3-[1-(4-tert-butylbenzyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]benzoyl}tyrosinamide,  
[M + H] = 574;
- 5 N-{5-[1-(4-tert-butylbenzyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]pentanoyl}tyrosinamide,  
[M + H] = 554;
- N-[3-(1-butyl-3-isoquinolin-3-yl-1H-pyrazol-5-yl)benzoyl]tyrosinamide, [M + H] =  
534;
- N-{4-[1-butyl-3-(2-furyl)-1H-pyrazol-5-yl]benzoyl}tyrosinamide, {M+H} = 473;
- 10 N-{5-[1-butyl-3-(2-furyl)-1H-pyrazol-5-yl]pentanoyl}tyrosinamide, [M+H] = 453;
- N-{3-[3-(2-furyl)-1-(4-isopropylphenyl)-1H-pyrazol-5-yl]propanoyl}tyrosinamide,  
{M+H} = 487;
- N-(4-{1-(4-tert-butylphenyl)-3-[3-(dimethylamino)phenyl]-1H-pyrazol-5-  
yl}benzoyl)tyrosinamide, [M+H] = 602;
- 15 N-[1-(aminocarbonyl)-3-(4-hydroxyphenyl)propyl]-4-[3-(2-furyl)-1-(4-  
isopropylphenyl)-1H-pyrazol-5-yl]benzamide, [M+H] = 549;
- N-[1-(aminocarbonyl)-3-(4-hydroxyphenyl)propyl]-5-{1-(4-tert-butylphenyl)-3-[3-  
(dimethylamino)phenyl]-1H-pyrazol-5-yl}pentanamide, [M+H] = 596;
- N-{5-[1-(4-tert-butylphenyl)-3-(2-furyl)-1H-pyrazol-5-yl]pentanoyl}tyrosinamide,  
20 [M+H] = 529;
- N-[1-(aminocarbonyl)-3-(4-hydroxyphenyl)propyl]-4-[3-(2-furyl)-1-pyridin-2-yl-1H-  
pyrazol-5-yl]benzamide, [M+H] = 508;
- N-(4-{3-[3-(dimethylamino)phenyl]-1-pyridin-2-yl-1H-pyrazol-5-  
yl}benzoyl)tyrosinamide, [M+H] = 547;
- 25 N-(5-{1-butyl-3-[3-(dimethylamino)phenyl]-1H-pyrazol-5-yl}pentanoyl)  
tyrosinamide, [M+H] = 506;
- N-(5-{1-(4-tert-butylphenyl)-3-[3-(dimethylamino)phenyl]-1H-pyrazol-5-  
yl}pentanoyl)tyrosinamide, [M+H] = 582;
- N-[5-(1-butyl-3-quinolin-3-yl-1H-pyrazol-5-yl)pentanoyl]tyrosinamide, [M+H] =  
30 514;
- N-{5-[1-(4-tert-butylphenyl)-3-quinolin-3-yl-1H-pyrazol-5-yl]pentanoyl}  
tyrosinamide, [M+H] = 590;
- N-[5-(1-butyl-3-quinolin-6-yl-1H-pyrazol-5-yl)pentanoyl]tyrosinamide, [M+H] =

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- 514;  
 N-{5-[1-(4-tert-butylphenyl)-3-quinolin-6-yl-1H-pyrazol-5-yl]pentanoyl}  
 tyrosinamide, [M+H] = 590;  
 N-{5-[1-(4-tert-butylbenzyl)-3-quinolin-6-yl-1H-pyrazol-5-yl]pentanoyl}  
 5 tyrosinamide, [M+H] = 604;  
 N-[5-(1-hexyl-3-pyrazin-2-yl-1H-pyrazol-5-yl)pentanoyl]tyrosinamide, [M+H] = 493;  
 N-[(1-butyl-3-pyridin-3-yl-1H-pyrazol-5-yl)methyl]glycyltyrosinamide; [M+H] =  
 451;  
 N-{[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]methyl}  
 10 glycyltyrosinamide, [M+H] = 527;  
 N-[(1-butyl-3-pyridin-3-yl-1H-pyrazol-5-yl)methyl]-beta-alanyltyrosinamide, [M+H]  
 = 465;  
 N-(3-{[(1-butyl-3-pyridin-3-yl-1H-pyrazol-5-yl)methyl]amino}benzoyl)tyrosinamide,  
 [M+H] = 513;  
 15 N-[3-({[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-  
 yl]methyl}amino)benzoyl]tyrosinamide, [M+H] = 589;  
 N-({1-[(1-butyl-3-pyridin-3-yl-1H-pyrazol-5-yl)methyl]piperidin-4-yl}carbonyl)  
 tyrosinamide, [M+H] = 505;  
 N-[(1-{[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]methyl}piperidin-4-  
 20 yl)carbonyl]tyrosinamide, [M+H] = 581;  
 N-2--{[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]methyl}-N~1~-[2-(4-  
 hydroxyphenyl)ethyl]glycinamide; [M+H] = 484;  
 N-3-[(1-butyl-3-pyridin-3-yl-1H-pyrazol-5-yl)methyl]-N~1~-[2-(4-  
 hydroxyphenyl)ethyl]-beta-alaninamide, [M+H] = 422;  
 25 4-{[(1-butyl-3-pyridin-3-yl-1H-pyrazol-5-yl)methyl]amino}-N-[2-(4-  
 hydroxyphenyl)ethyl]benzamide, [M+H] = 470.

#### Example 5: Regioselective synthesis of pyrazoles

- Commercially available Fmoc-protected rink amide resin (0.7g) was  
 30 deprotected with 20% piperidine in DMF, rinsed and acylated with 0.5M solution of  
 Fmoc-amino acid (10 equiv)/HATU (10 equiv)/DIEA (20equiv) overnight in DMF at  
 room temperature, rinsed with DMF. Fmoc group was removed with 20%  
 piperidine/DMF and resin was rinsed with DMF, acylated with 0.5M solution of

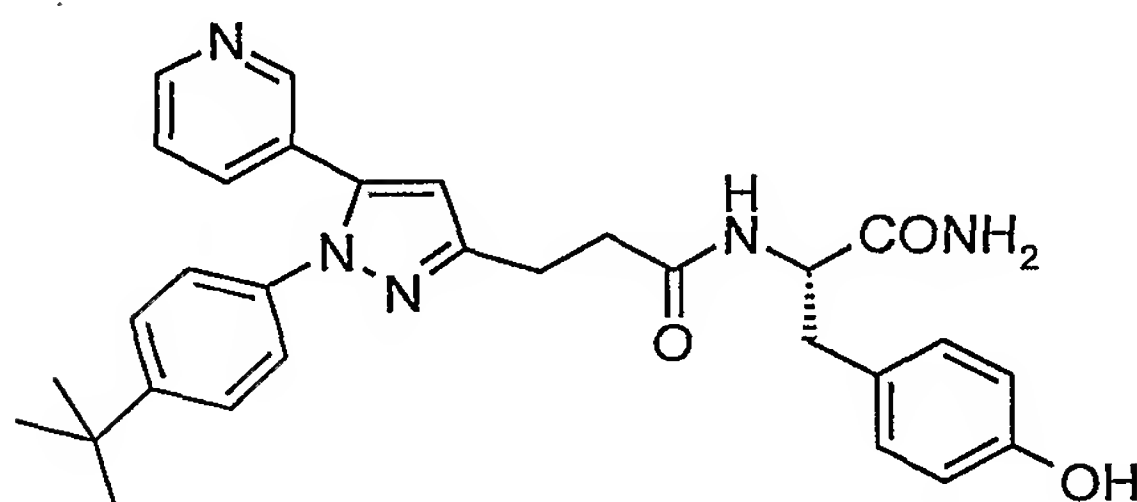
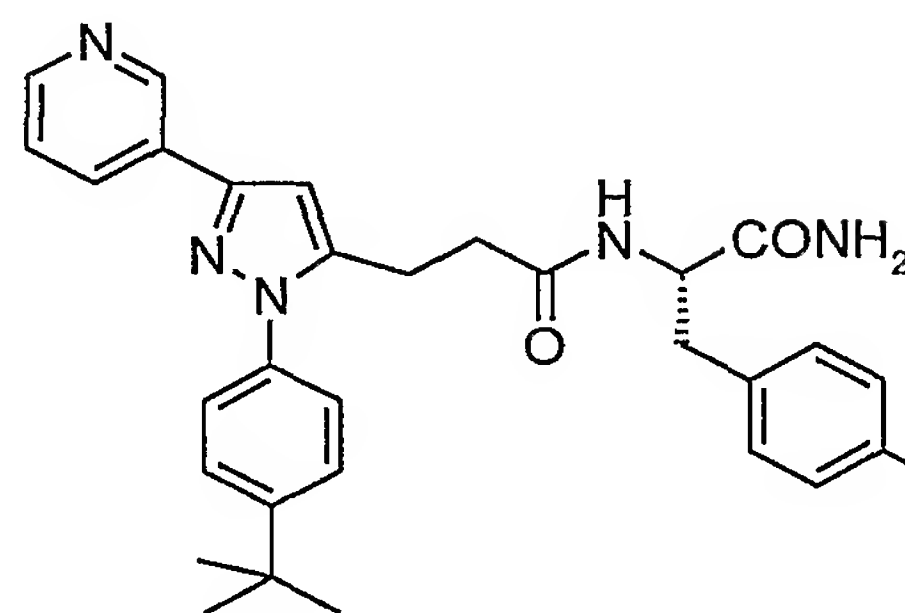


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acetyl carboxylic acid (10 equiv)/HATU (10 equiv)/DIEA (20equiv) overnight at room temperature, rinsed with DMF. The resin was added with LiOH.H<sub>2</sub>O (40 equivalents) in anhydrous DME and 40 equivalents of aldehyde was added. The resin was shaken for 16 hrs and filtered and washed with glacial acetic acid, DMA, i-PrOH, DCM. The resulted  $\alpha,\beta$ -unsaturated ketone was cyclized to pyrazole by adding the 0.5M solution of 4-*t*-butyl phenyl hydrazine in DMSO and allowing the reaction to proceed for 16 hrs. Resin was washed with DMA, i-PrOH, DCM and dried before treating with TFA release the desired pyrazole product from the resin. The crude product was purified by preparative HPLC.

#### Example 6: Solution phase synthesis

Synthesis of N-(3-[1-(4-*tert*-butylphenyl)-5-pyridin-3-yl-1H-pyrazol-3-yl]propanoyl)tyrosinamide (3-A) and N-(3-[1-(4-*tert*-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]propanoyl)tyrosinamide (3-B)

3-A3-B

Compound 3-A: 6-Hydroxy-1-(3-pyridinyl)-hexan-1,3-dione

A solution of  $\gamma$ -butyrolactone (1.92 mL, 2.15 g, 25.0 mmol), 60% suspension of sodium hydride in mineral oil (300 mg, 7.50 mmol) and 3-acetylpyridine (551  $\mu$ L, 606 mg, 5.00 mmol) in dimethylsulfoxide (4 mL) and tetrahydrofuran (36 mL) was stirred overnight at 25 °C. Ethanol (4 mL) was added to destroy excess sodium hydride and the reaction mixture was adsorbed on silica gel (10 g). Flash chromatography on silica gel (75 g), eluting with DCM/MeOH/NH<sub>4</sub>OH (96/4/1), gave

- 50 -

1.14 g of a yellow oil containing compound 3-A (0.62 g, 60%) .

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ) :  $\delta$  9.00 (d,  $J = 1.8$  Hz, 1H), 8.65 (dd,  $J = 4.8, 1.5$  Hz, 1H), 8.09 (dt,  $J = 8.1, 2.2$  Hz, 1H), 7.34 (dd,  $J = 8.1, 4.8$  Hz, 1H), 6.17 (s, 1H), 3.64 (t,  $J = 6.2$ , 2H), 2.5 (m, 2H), 1.88 (t,  $J = 6.2$ , 2H).

5 MS (ESI, +) : 208 ( $M + 1$ )

Compound 3-B: 3-{1-(4-*tert*-butylphenyl)-5-pyridin-3-yl-1H-pyrazol-3-yl}propan-1-ol and 3-{1-(4-*tert*-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl}propan-1-ol .

10 A solution of compound 3-A (370 mg, 1.79 mmol) and 4-*tert*-butylphenylhydrazine hydrochloride (359 mg, 1.79 mmol) in absolute methanol (10 mL) was stirred overnight at 25 °C. The reaction mixture was then adsorbed on silica gel (5 g) and purified by flash chromatography on silica gel (60 g), eluting with DCM/MeOH/ $\text{NH}_4\text{OH}$  (96/4/1), to afford 709 mg of a yellow oil containing the  
15 pyrazole 3-B (two regioisomers, 452 mg, 75%, ratio 24/76) and DMSO. An aliquot of this mixture was purified with preparative HPLC deltapack C18 column, using a gradient of water/acetonitrile from 95/5 to 50/50 in 60 min, to give pure samples of the two regioisomers.

20 More polar regioisomer :

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ) :  $\delta$  8.80 (s, 1H), 8.76 (d,  $J = 5.0$  Hz, 1H), 7.95 (d,  $J = 8.1$ ), 7.70 (dd,  $J = 8.1, 5.4$  Hz, 1H), 7.43 (d,  $J = 7.7$  Hz, 2H), 7.16 (d,  $J = 8.1$  Hz, 2H), 6.60 (s, 1H), 4.48 (t,  $J = 6.0$  Hz, 2H), 2.88 (t,  $J = 7.3$  Hz, 2H), 2.23 (pent.,  $J = 7.0$  Hz, 2H), 1.32 (s, 9H).

25 MS (ESI, +) : 336 ( $M + 1$ )

Less polar regioisomer (partially salified with trifluoroacetate) :

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ) :  $\delta$  9.30 (d,  $J = 9.2$  Hz, 1H), 8.87 (d,  $J = 8.4$  Hz, 1H), 8.73 (t,  $J = 5.8$  Hz, 1H), 7.9 (m, 1H), 7.5 (m, 2H), 7.3 (m, 2H), 6.81 (s, 0.6H), 6.77 (s, 0.4H), 4.36 (t,  $J = 6.0$  Hz, 1.2H), 3.71 (t,  $J = 6.0$  Hz, 0.8H), 2.83 (t,  $J = 7.7$  Hz, 1.2H), 2.81 (t,  $J = 8.0$  Hz), 2.10 (pent.,  $J = 7.7$  Hz, 1.2H), 1.92 (pent.,  $J = 7.3$  Hz, 0.8H), 1.36 (s, 9H).

MS (ESI, +) : 336 ( $M + 1$ )

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Compound 3-C: 3-{1-(4-*tert*-butylphenyl)-5-pyridin-3-yl-1H-pyrazol-3-yl}propanoic acid and 3-{1-(4-*tert*-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl}propanoic acid

To a solution of pyrazoles 3-B (168 mg, 0.500 mmol) in acetone (4 mL) was added a  
5 solution of 2N H<sub>2</sub>Cr<sub>2</sub>O<sub>7</sub> (0.75 mL) at 10 °C. The mixture was stirred for 1 h, and the solution was decanted away from solid, concentrated and filtrated through a C<sub>18</sub> column with a mixture 95/5 of water/acetonitrile. Once concentrated, the residue was engaged directly into the next step.

MS (ESI, +) : 350 (M + 1)

10

Compound 3 : N-(3-[1-(4-*tert*-butylphenyl)-5-pyridin-3-yl-1H-pyrazol-3-yl]propanoyl)tyrosinamide (3-A) and N-(3-[1-(4-*tert*-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]propanoyl)tyrosinamide (3-B)

15 To a solution of compounds 3-C (150 mg, 0.43 mmol), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (104 mg, 0.54 mmol), HOAT (73 mg, 0.54 mmol) and *N,N*-diisopropylethylamine (229 µL, 174 mg, 1.35 mmol) in *N,N*-dimethylformamide (3 mL) was added *O*-(*tert*-butyl)tyrosinamide (128 mg, 0.54 mmol). The reaction mixture was stirred overnight at 25 °C, then diluted with a  
20 solution of 0.1N ammonia (30 mL) and extracted with ethyl acetate (3 x 25 mL). The combined organic phases are dried over magnesium sulfate, filtrated and concentrated. The crude thus obtained was dissolved in dichloromethane (5 mL) and stirred overnight at room temperature in presence of trifluoroacetic acid (2 mL). The reaction mixture was concentrated and injected on HPLC deltapack C18 column for  
25 purification using a linear gradient of 0.1% TFA water/acetonitrile from 95/5 to 60/40 in 60 min to give the two possible regioisomers whose structures were assigned by analogy with compounds 1-A and 1-B.

N-(3-[1-(4-*tert*-butylphenyl)-5-pyridin-3-yl-1H-pyrazol-3-yl]propanoyl)tyrosinamide (3-A) :

30 <sup>1</sup>H NMR (DMSO): δ 8.54 (s, 1H), 8.45 (s, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 8.1 Hz, 1H), 7.42 (m, 3H), 7.38 (s, 1H), 7.16 (d, J = 7.3 Hz, 2H), 7.01 (d, J = 8.1 Hz, 2H), 7.00 (s, 1H), 6.61 (d, J = 7.0 Hz, 2H), 6.56 (s, 1H), 4.38 (m, 1H), 2.90 – 2.75 (m, 3H), 2.64 (dd, J = 13.9, 9.9 Hz, 1H), 2.50 (m, 2H), 1.28 (s, 9H).

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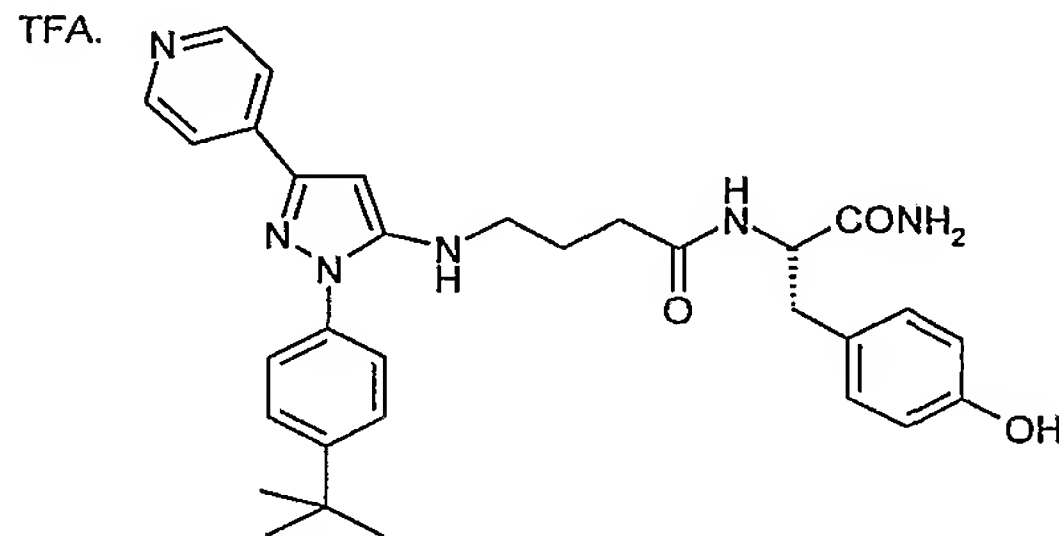
MS (ESI, +): 512 (M + 1)

N-(3-[1-(4-*tert*-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]propanoyl)tyrosinamide (3-B) :

- 5  $^1\text{H}$  NMR (DMSO):  $\delta$  9.15 (s, 1H), 8.68 (s, 1H), 8.51 (d,  $J = 7.3$  Hz, 1H), 8.13 (d,  $J = 8.5$  Hz, 1H), 7.76 (m, 1H), 7.58 (d,  $J = 8.4$  Hz, 2H), 7.47 (d,  $J = 8.4$  Hz, 2H), 7.44 (s, 1H), 7.02 (s, 1H), 6.99 (d,  $J = 8.4$  Hz, 2H), 6.93 (s, 1H), 6.58 (d,  $J = 8.4$  Hz, 2H), 4.34 (m, 1H), 2.88 – 2.79 (m, 3 H), 2.63 (dd,  $J = 14.3, 10.2$  Hz, 1H), 2.50 (m, 3H) 1.34 (s, 9H).
- 10 MS (ESI, +): 512 (M + 1)

Example 7: Synthesis of the trifluoroacetate salt of N-(4-{[1-(4-*tert*-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]amino}butanoyl)tyrosinamide 7

15

7

- 20 Compound 7a : : N-[1-(4-*tert*-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]-trifluoroacetamide

N-[1-(4-*tert*-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]-amine (1.05g, 3.60mmol) obtained following literature procedure (J.Chem.Research(S), 10,1992) was dissolved in pyridine, trifluoroacetic anhydride (530  $\mu\text{l}$ , 3.78 mmol) was then slowly added and  
 25 the mixture was stirred under nitrogen atmosphere at room temperature for 12 h. Pyridine was concentrated under reduced pressure and the resulting brown oil was dissolved in Ethyl acetate and washed twice with water and twice with brine. The

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organic layer was dried over magnesium sulfate, filtered and concentrated to give 1.17 g of crude material. This crude was purified by flash chromatography with DCM/MeOH/NH<sub>4</sub>OH (95/5/1 then 85/5/1). 387 mg (yield = 28%) of pure material was isolated beside degradations products.

5 <sup>1</sup>H NMR (CDCl<sub>3</sub>) : 1.34 (s, 9H), 7.21 (s, 1H), 7.41 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 8.7 Hz, 2H), 7.72 (m, 2H), 8.47 (m, 1H), 8.58 (m, 2H).

MS (ESI, +) : 389 (M+1)

Compound 7b : 4-{[1-(4-*tert*-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]}(trifluoroacetyl)amino}butanoic acid

10 A solution of compound 7a (387mg, 1.0 mmol) and ethyl-4-bromobutyrate (780mg, 4 mmol) in acetone (15 mL) was heated under reflux in presence of potassium carbonate (553mg, 4.0mmol) and potassium iodide (183mg, 1.1mmol). After 48h, the reaction was completed, acetone was removed under reduced pressure and the crude was

15 dissolved in Ethyl acetate, washed with water and brine (2x) and finally dried over magnesium sulfate, filtrated and concentrated.

The crude (930mg) was purified by flash chromatography with DCM/MeOH/NH<sub>4</sub>OH 90/10/1. 354 mg of a nice yellow powder were isolated (yield = 70%).

1H NMR (CDCl<sub>3</sub>) : 1.25 (t, J = 6.2 Hz, 3H), 1.35 (s, 9H), 2.12 (m, 2H), 2.35 (t, J = 6.6 Hz, 2H), 4.12 (q, J = 6.2 Hz, 2H), 4.34 (t, J = 7.3 Hz, 2H), 7.21 (s, 1H), 7.45 (d, J = 7.7 Hz, 2H), 8.03 (m, 4H), 8.31 (d, J = 6.2 Hz, 2H).

MS (ESI, +) : 503 (M+1)

Compound 7c: Potassium salt of 4-{[1-(4-*tert*-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]amino}butanoic acid

25 A solution of ester 7b ( 234mg, 0.47mmol) in methanol/water, (1:1, 10mL) was heated under reflux for 8h in presence of potassium carbonate (195 mg, 1.41mmol). The mixture was then concentrated under reduced pressure, toluene was added and removed under reduced pressure. The crude thus obtained (398mg) was analyzed (see

30 below) and directly engaged in the next step.

1H NMR (DMSO) : 1.34 (s, 9H), 1.82 (t, J = 6.2 Hz, 2H), 2.01 (t, J = 6.3 Hz, 2H), 4.55 (t, J = 6.6 Hz, 2H), 5.75, s, 1H), 6.32 (s, 1H), 7.58 (s, 4H), 8.33 (d, J = 5.1 Hz,



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2H), 8.98 (d,  $J = 5.5$  Hz, 2H).

MS (ESI, +) : 379 (M+1)

5 Compound 7d : O-(*tert*-butyl)tyrosinamide

N-Fmoc-O-*tert*-butyl-tyrosine (3.27g, 7.12mmol) was dissolved in dioxane (15 mL). Ammonium hydrogenocarbonate (732mg, 9.26mmol), di-*tert*-butyl-dicarbonate (2.02g, 9.26 mmol) and pyridine (0.4 mL) were added and the mixture was stirred  
10 under nitrogen atmosphere at room temperature for 12h. It was then diluted with ethyl acetate and the organic phase was washed with brine (2x), 5% sulfuric acid (1x) and brine again. It was dried over magnesium sulfate and concentrated. The crude thus obtained (3.17g) was dissolved in dichloromethane (50 mL) and diethylamine (10 mL). The mixture was stirred at room temperature for 12h, concentrated under  
15 reduced pressure and purified by flash chromatography with DCM/MeOH/NH<sub>4</sub>OH (95/5/1 then 90/10/1) to give 1.37 g of the desired compound (yield = 81%).  
<sup>1</sup>H NMR (CDCl<sub>3</sub>) : 1.32 (s, 9H), 2.66 (dd,  $J = 9.5$  and 13.6 Hz, 1H), 3.20 (dd,  $J = 3.7$  and 13.9 Hz, 1H), 3.57 (dd,  $J = 4.0$  and 9.5 Hz, 1H), 5.40 (m, 1H), 6.93 (d,  $J = 7.0$  Hz, 2H), 7.06 (m, 1H), 7.10 (d,  $J = 7.3$  Hz, 2H).  
20 MS (ESI, +) : 237 (M+1)

Compound 7e: N-(4-{[1-(4-*tert*-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]amino}butanoyl) -O-(*tert*-butyl)tyrosinamide

25 Compound 7c (170 mg, 0.45mmol) was reacted with 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (104 mg, 0.54mmol), HOAT (73mg, 0.54mmol) and diisopropylamine (230μl, 1.35mmol) in dimethylformamide (6 mL). O-(*tert*-butyl)tyrosinamide 7d (118mg, 0.50mmol) was then added and the reaction mixture was stirred at room temperature under nitrogen atmosphere. After  
30 completion of the reaction (48h), it was diluted with ethyl acetate and water. The two layers were separated and it appeared that the product was essentially in the aqueous phase. This latter was concentrated and injected on HPLC deltapack C18 column for purification using a gradient of water/acetonitrile from 95/5 to 40/60 in 60min. 96 mg of pure compound was isolated after lyophilisation (yield = 36%).



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<sup>1</sup>H NMR (CDCl<sub>3</sub>) : 1.25 (s, 9H), 1.35 (s, 9H), 2.20-2.43 (m, 4H), 2.90 (t, J = 9.9 Hz, 1H), 3.18 (brd, J = 10.6 Hz, 1H), 4.27-4.52 (m, 7H), 6.20 (s, 1H), 6.84 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 7.50 (m, 4H), 8.18 (m, 2H), 8.29 (m, 1H), 8.53 (m, 1H).  
MS (ESI, +) : 597 (M+1)

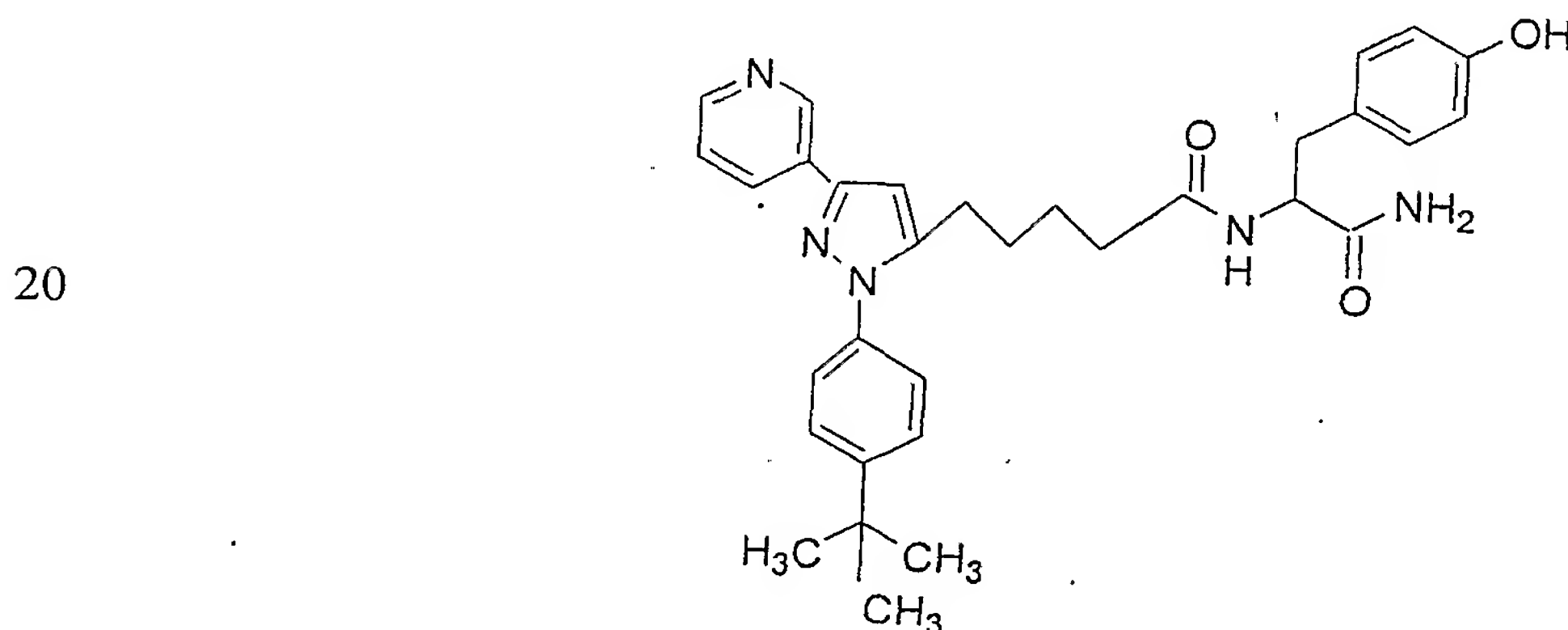
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Compound 7: Compound 7e (89 mg, 0.15 mmol) was dissolved in dichloromethane and trifluoroacetic acid was added. The mixture was stirred overnight and concentrated to give 103 mg of a brown solid (quantitative yield).

<sup>1</sup>H NMR (DMSO) : 0.82 (m, 2H), 1.33 (s, 9H), 2.13 (m, 2H), 2.60 (m, 1H), 2.86 (m, 1H), 4.19-4.38 (m, 3H), 5.81 (m, 1H), 6.32 (s, 1H), 6.63 (d, J = 6.6 Hz, 2H), 7.00 (d, J = 6.6 Hz, 2H), 7.01 (s, 1H), 7.45 (s, 1H), 7.58 (brs, 4H), 7.69 (m, 2H), 8.02 (d, J = 8.4 Hz, 1H), 8.34 (d, J = 5.1 Hz, 2H), 8.85 (d, J = 5.1 Hz, 2H), 9.16 (s, 1H).

#### Example 8: CHO parental cells assay.

The following compound 1-B was demonstrated to be hFSHR specific by testing it on untransfected CHO parental cells.



25

1-B

Briefly CHO parental cells were plated in 96 well packard view plates 5 x 10<sup>4</sup> cells/well in serum containing media. After 20 hours the cells were confluent. The wells were washed with serum free assay medium (containing 0.1mM MIX) and pre-incubated for 15 minutes in this medium. Compound 1 and forskolin (positive control) were added and the cells were incubated for an additional one hour. The cells were lysed and intracellular cAMP was measured using the Amersham direct one step cAMP-RIA kit according to the manufacturers directions. Compound 1 showed no response over background.

These cells were shown to have no response over background to stimulation with a  $10^{-7}$  (M) dose of rhFSH in a previous experiment. In both experiments forskolin showed a five fold response over background.

5

#### Example 9: FSH Assay Method

All compounds were stored in 96-well deepwell plates in DMSO at a nominal concentration of 10mM (assuming perfect synthesis and yields). Compounds were screened for agonist activity at the FSH receptor using the recombinant FSH receptor stably transfected and expressed in Chinese Hamster Ovary Cells (CHO cells) essentially as described in the work by Kelton, et al. (Molecular and Cellular Endocrinology, 1992, 89, 141-151). Since the FSH receptor is known to act via a G-protein (Gs) to activate adenylyl cyclase and hence raise intracellular levels of cAMP the high throughput screening (HTS) assay used a gene reporter system consisting of the cAMP response element coupled upstream to the reporter gene which, in this case was the enzyme luciferase. Thus an agonist at the FSH receptor increases cAMP in the cell which results in activation of the CREB (cAMP) response element binding protein). This molecule interacts with the CRE element on the gene in the nucleus and results in increased transcription of the genes downstream of this element. The substrate for the enzyme (Packard Instrument Company 800 Research Parkway, Meriden, CT 06450, USA) was added to the cells after appropriate incubation with the compounds or FSH and the amount of luciferase expressed was measured by quantitating the luminescence produced by the enzyme using a TopCount scintillation/luminescence counter running in single photon counting mode. A compound which acted as an agonist at the receptor should produce light from the treated cells in proportion to its concentration within the incubation. Luminescence should be saturable at high concentrations of the compound.

25

#### Example 10: HTS Primary Assay.

30

The compounds, in deepwell plates (Master plates) as indicated above were loaded on the robotic deck along with the appropriate number of assay plates and daughter plates. A 10  $\mu$ l aliquot from each master plate was transferred to the corresponding daughter plate and 90  $\mu$ l of DME/F12 was added and mixed within

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each well. 20  $\mu$ l was then removed from the daughter plate and dispensed into the assay plate. After addition of an aliquot of FSH (equivalent to an EC100 response for this hormone [Final concentration of 5c-11M]) to each of three wells on the plate, 80ul of media (DME/F<sup>12</sup>+ 2% serum) and 100ul aliquot of cells ( $4 \times 10^5$ /ml in the same media) were added and the plate incubated at 37°C for 3 hrs 30 min. At this time the plate was removed from the incubator and media in each well was aspirated and the cells adhering to the bottom of the plate washed with 300ul PBS containing 1mM  $Ca^{2+}$  and 1mM  $Mg^{2+}$ . The PBS was aspirated and 100ul PBS added to each well. 100ul of Lucite (prepared as described by the manufacturer) was added to each well and the plate was shaken gently for 40 seconds prior to placement in the TopCount plate reader. After allowing 3.5 minutes for the plate to dark-adapt within the machine, the amount of luminescence generated was quantiated using Single Photon Counting mode. The data was transmitted electronically from the TopCount to the robot processing computer terminal and was renamed with an ID corresponding to the original master plate ID. Data was evaluated using an Excel macro and compounds showing activity comparable to that produced by an EC100 of FSH itself were further analyzed in the same assay at differing concentrations. LDR (log-dose-response) curves were generated for these compounds in CHO cells containing the FSH receptor and these curves were also compared with those in either cells expressing a different Gs linked receptor or in cells lacking any transfected receptor and these curves were also compared with those in either cells expressing a different Gs linked receptor or in cells lacking any transfected receptor.

Compounds which showed receptor specificity and activity at low concentrations were progressed to secondary assays which included dose-response curves in Y1 cells co-expressing the human FSH receptor or in isolated rat granulosa cells.

#### Example 11: Secondary Assay; Rat Granulosa Cell Assay

A primary rat granulosa cell bioassay for follicle stimulating hormone (FSH) was used. Conversion of testosterone to estradiol in the presence of low nanomolar concentrations of FSH was detected using this assay. In this *in vitro* assay, conversion of androstendione to estrogen by granulosa cells in the presence of FSH

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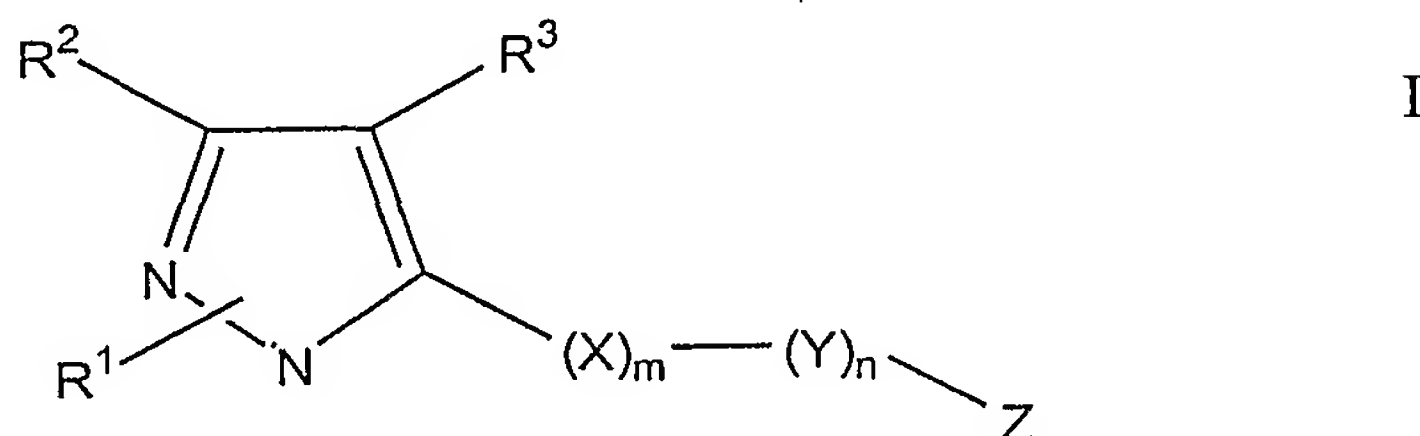
was measured using a RIA.

Granulosa cell culture and FSH stimulation: Cells were plated at 5000, 8,000 and 20,000 cells/well/ 200  $\mu$ l of GAB medium on poly-D-lysine coated 96-well tissue culture plates. Plates were incubated at 37°C in a 5% CO<sub>2</sub>/95% air incubator for 3 days. Cultures were washed prior to stimulation with FSH or LH. 50 $\mu$ l of 4X concentrations of rhFSH, rhLH or forskolin was added to the cultures. To define the range of the dose response curve the rhFSH was diluted so that the final concentration on the cells was between  $10^{-7}$  to  $10^{-15}$  (M) with three doses per log at 1, 2 and 5. Forskolin was diluted so that the final concentration on the cells was 1 $\mu$ M. Cells were incubated @ 37°C in 5% CO<sub>2</sub>. Three days later, cell supernatants were collected and diluted 1:100 in GAB medium for measurement of estradiol by RIA. The RIA was performed according to manufacturer directions except that an estradiol standard was prepared in absolute ethanol at 100ng/ml and then further diluted in GAB medium, instead of kit buffer. The concentration of hormone was plotted on the X-axis against the amount of estradiol produced by the cells on the Y-axis using Origin graphics software.

The invention has been described in detail with reference to preferred embodiments thereof. However, it will be appreciated that those skilled in the art, upon consideration of this disclosure, may make modifications and improvements within the spirit and scope of the invention.

What is claimed is:

1. A method for treating infertility in a mammal, comprising administering to a mammal suspected of infertility a therapeutically effective amount of a substituted pyrazole compound.
2. A method of claim 1 wherein pyrazole is substituted at 1 or 2 ring positions by non-hydrogen substituents.
3. A method of claim 1 wherein the pyrazole is substituted at the 5-position by a non-hydrogen substituent.
4. A method of claim 1 wherein the pyrazole is substituted at both the 3- and 5-positions by non-hydrogen substituents.
5. A method of any one of claims 1 through 4 wherein the pyrazole compound is of the following Formula I:



wherein R<sup>1</sup> is hydrogen; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group;

R<sup>2</sup> and R<sup>3</sup> are each independently hydrogen, halogen, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted alkylthio; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl



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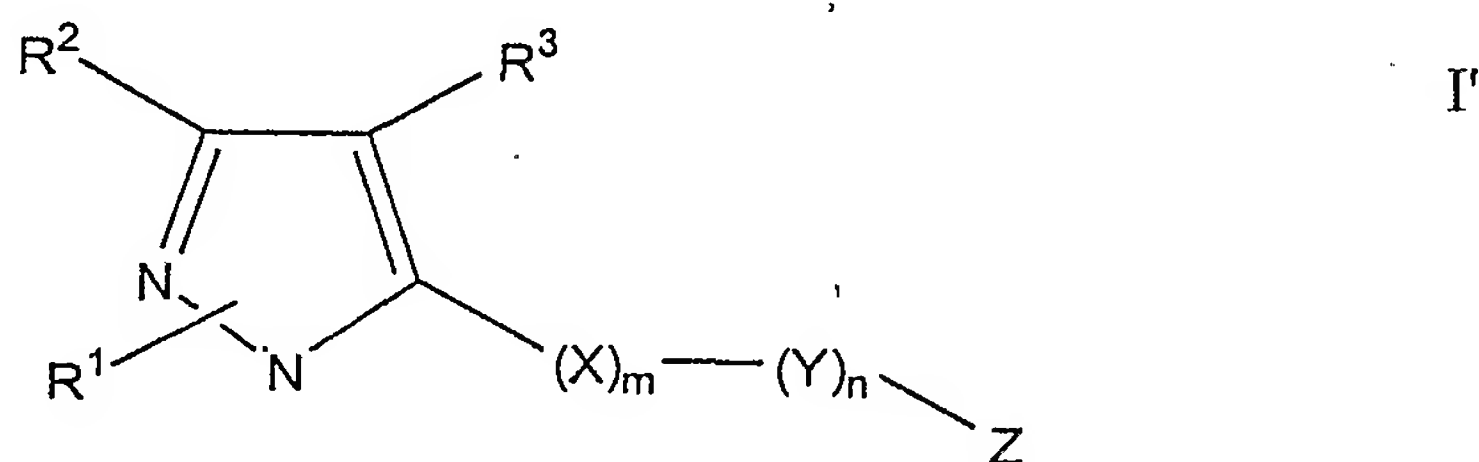
group;

X is optionally substituted alkylene; optionally substituted alkenylene; optionally substituted alkynylene; optionally substituted heteroalkylene; optionally substituted heteroalkenylene; optionally substituted heteroalkynylene; or X is optionally alicyclic, optionally substituted carbocyclic aryl; optionally substituted heteroalicyclic, optionally substituted heteroaromatic, optionally substituted heteroaralkyl, or optionally substituted heteroalicyclicalkyl group;

Y is optionally substituted amino; optionally substituted methylene; carbonyl; or sulfonyl;

Z is an optionally substituted alkylamine; an amino acid; or a glycine; m is 0 or 1; n is 0 or 1; and pharmaceutically acceptable salts thereof.

6. A method of any one of claims 1 through 4 wherein the pyrazole compound is of the following Formula I':



wherein R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are each independently hydrogen; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted alkylthio; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl;

X is optionally substituted alkylene; optionally substituted alkenylene; optionally substituted alkynylene; optionally substituted heteroalkylene; optionally substituted heteroalkenylene; optionally substituted heteroalkynylene; optionally substituted alicyclic; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic; optionally substituted heteroalicyclic group; optionally substituted heteroaralkyl; or optionally substituted heteroalicyclicalkyl group;

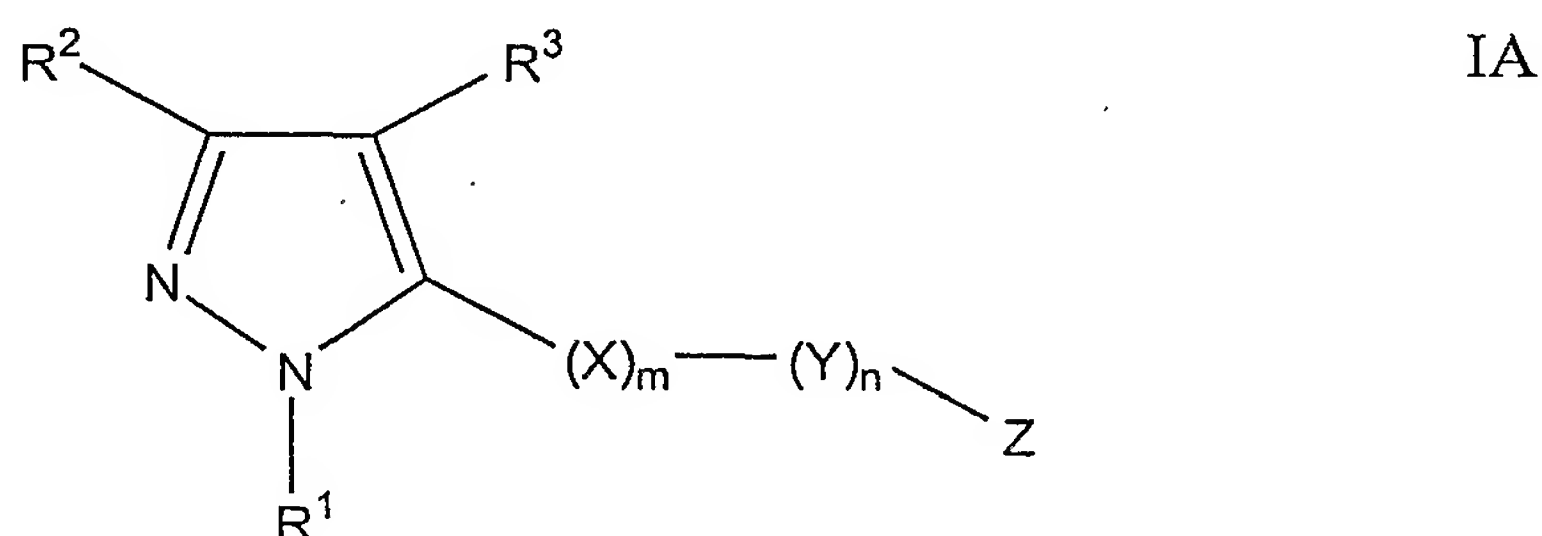


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Y is optionally substituted amino; optionally substituted methylene; carbonyl; or sulfonyl;

Z is an optionally substituted alkylamine; an amino acid; or a glycine; m and n are each independently 0 or 1; and pharmaceutically acceptable salts thereof.

7. A method of any one of claims 1 through 4 wherein the pyrazole compound is of the following Formula IA:



wherein R<sup>1</sup> is optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic; optionally substituted heteroalicyclic group; optionally substituted heteroaralkyl; or optionally substituted heteroalicyclicalkyl group;

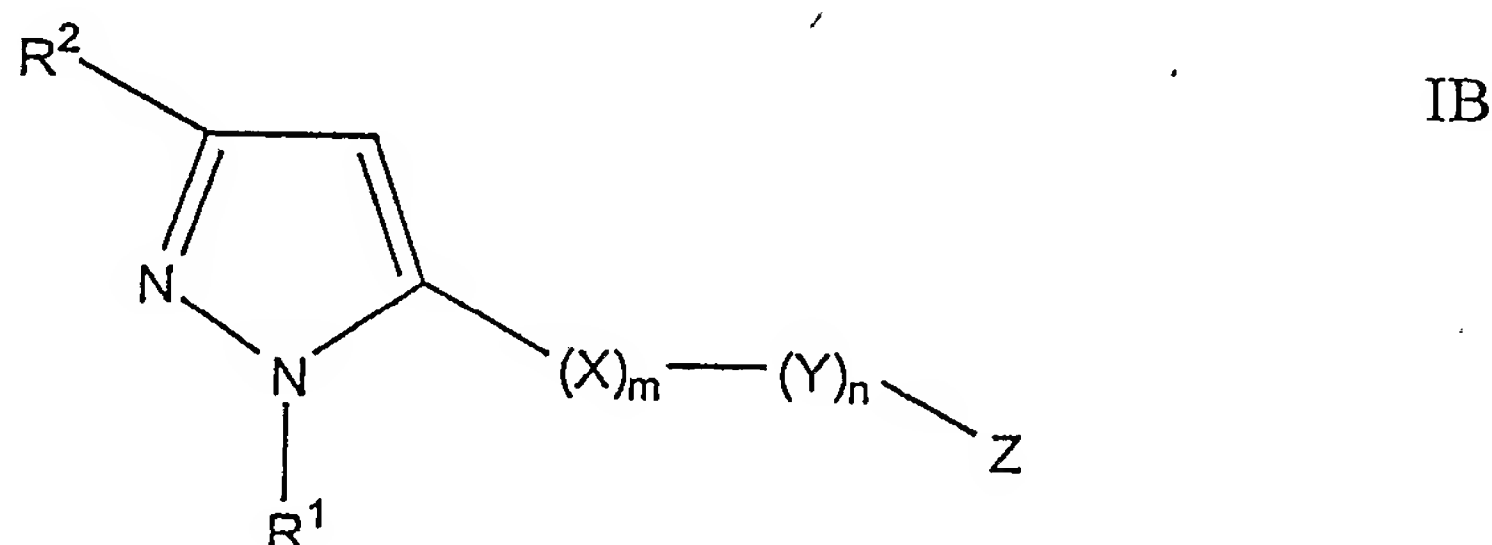
R<sup>2</sup> and R<sup>3</sup> are each independently hydrogen; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted alkylthio; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl;

X is optionally substituted alkylene; optionally substituted alkenylene; optionally substituted alkynylene; optionally substituted heteroalkylene; optionally substituted heteroalkenylene; optionally substituted heteroalkenynylene; optionally substituted alicyclic; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic; optionally substituted heteroalicyclic group; optionally substituted heteroaralkyl; or optionally substituted heteroalicyclicalkyl group;

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Z is an optionally substituted alkylamine; an amino acid; or a glycine; m and n are each independently 0 or 1; and pharmaceutically acceptable salts thereof.

8. A method of any one of claims 1 through 4 wherein the pyrazole compound is of the following Formula IB:



wherein R<sup>1</sup> and R<sup>2</sup> are, each independently optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group;

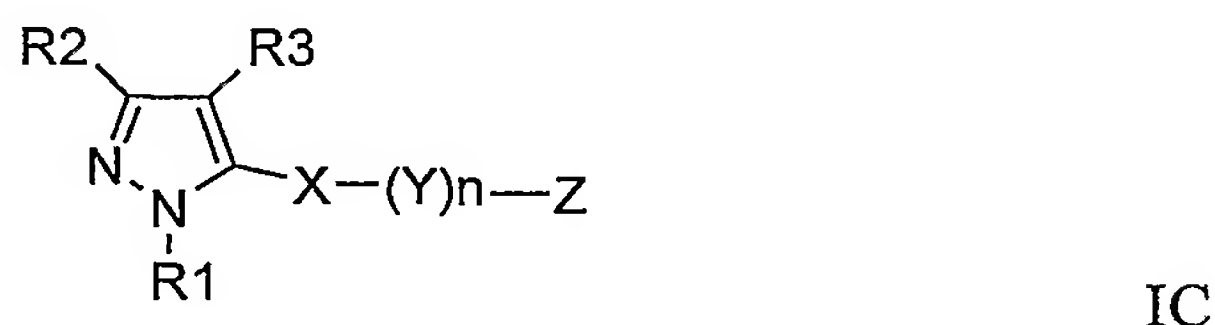
X is optionally substituted alkylene; optionally substituted alkenylene; optionally substituted alkynylene; optionally substituted heteroalkylene; optionally substituted heteroalkenylene; optionally substituted heteroalkenynylene; optionally substituted alicyclic; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic; optionally substituted heteroalicyclic group; optionally substituted heteroaralkyl; or optionally substituted heteroalicyclicalkyl group;

Y is optionally substituted amino; optionally substituted methylene; carbonyl; or sulfonyl;

Z is an optionally substituted alkylamine; an amino acid; or a glycine; m and n are each independently 0 or 1; and pharmaceutically acceptable salts thereof.

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9. A method of any one of claims 1 through 4 wherein the pyrazole compound is of the following Formula IC:



wherein R<sup>1</sup> is optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group;

R<sup>2</sup> is halogen; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted alkylthio; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group;

R<sup>3</sup> is hydrogen; halogen; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted alkylthio; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group;

Y is optionally substituted amino; optionally substituted methylene; carbonyl; or sulfonyl;

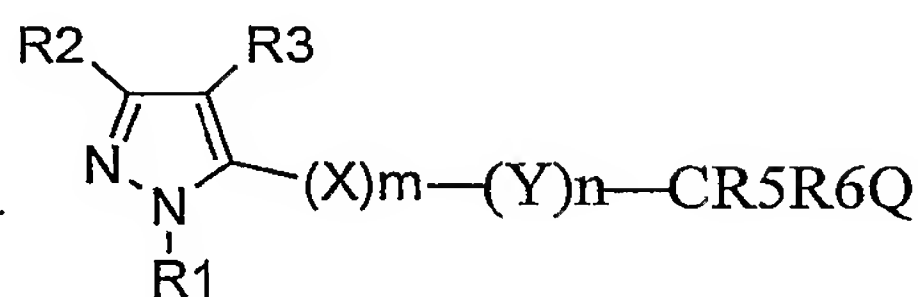
Z is an optionally substituted alkylamine; an amino acid; or a glycine;

n is 0 or 1;

X is optionally substituted heteroalkylene; optionally substituted heteroalkenylene; optionally substituted heteroalkynylene; and pharmaceutically acceptable salts thereof.

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10. A method of any one of claims 1 through 4 wherein the compound is of the following Formula ID



ID

wherein R<sup>1</sup> is hydrogen; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group;

R<sup>2</sup> is halogen; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted alkylthio; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group;

R<sup>3</sup> is hydrogen; halogen; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted alkylthio; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group;

X is optionally substituted alkylene; optionally substituted alkenylene; optionally substituted alkynylene; optionally substituted heteroalkylene; optionally substituted heteroalkenylene; optionally substituted heteroalkynylene; or X is optionally alicyclic, optionally substituted carbocyclic aryl; optionally substituted heteroalicyclic, optionally substituted heteroaromatic, optionally substituted heteroaralkyl, or optionally substituted heteroalicyclicalkyl group;

Y is optionally substituted amino; optionally substituted methylene; carbonyl; or sulfonyl;

Z is an optionally substituted alkylamine; an amino acid; or a glycine;

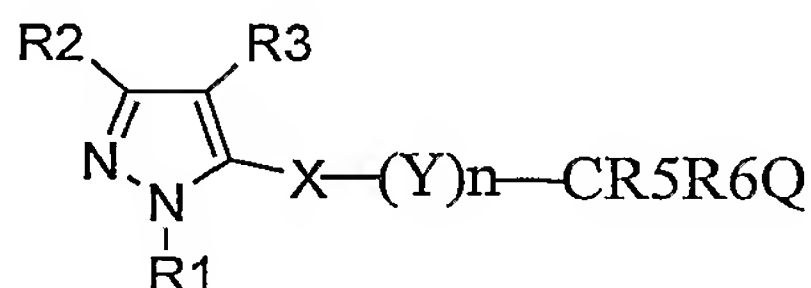
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n is 0 or 1;

R<sup>5</sup> and R<sup>6</sup> are independently hydrogen, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group;

Q is omitted or is  $-(CH_2)_p-CO-A-R^7$  wherein p is 0, 1 or 2 ; A is O or NH and R<sup>7</sup> is independently hydrogen, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group; and pharmaceutically acceptable salts thereof.

11. A method of any one of claims 1 through 4 wherein the compound is of the following Formula IE :



IE

wherein R<sup>1</sup> is optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group;

R<sup>2</sup> is halogen; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted alkylthio; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group;

R<sup>3</sup> is halogen, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted

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alkylthio; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group;

Y is optionally substituted amino; optionally substituted methylene; carbonyl; or sulfonyl;

Z is an optionally substituted alkylamine; an amino acid; or a glycine;

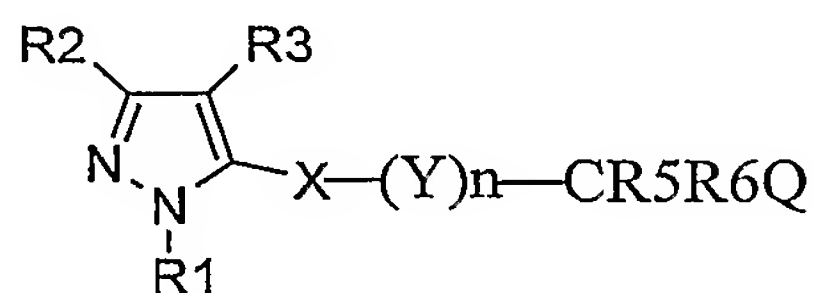
n is 0 or 1;

X is optionally substituted heteroalkylene; optionally substituted heteroalkenylene; optionally substituted heteroalkynylene;

R<sup>5</sup> and R<sup>6</sup> are independently hydrogen; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group; and

Q is omitted or is  $-(CH_2)_p-CO-A-R^7$  wherein p is 0, 1 or 2 ; A is O or NH and R<sup>7</sup> is independently hydrogen, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group; and pharmaceutically acceptable salts thereof.

12. A method of any one of claims 1 through 4 wherein the compound is of the following Formula IF:



IF



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wherein R<sup>1</sup> is optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group;

R<sup>2</sup> is halogen; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted alkylthio; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group;

R<sup>3</sup> is hydrogen; halogen; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted alkylthio; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group;

Y is optionally substituted amino; optionally substituted methylene; carbonyl; or sulfonyl;

Z is an optionally substituted alkylamine; an amino acid; or a glycine;

n is 0 or 1;

X is optionally alicyclic, optionally substituted carbocyclic aryl; optionally substituted heteroalicyclic, optionally substituted heteroaromatic, optionally substituted heteroaralkyl, or optionally substituted heteroalicyclicalkyl group;

R<sup>5</sup> and R<sup>6</sup> are independently hydrogen, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group; and

Q is omitted or is  $-(CH_2)_p-CO-A-R^7$  wherein p is 0, 1 or 2 ; A is O or NH and R<sup>7</sup> is independently hydrogen, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic

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group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group; and pharmaceutically acceptable salts thereof

13. A method of any one of claims 5 through 12 wherein  $R^1$ ,  $R^2$  and  $R^3$  is other than hydrogen.

14. A method of any one of claims 5 through 13 wherein  $R^2$  is other than hydrogen.

15. A method of any one of claims 5 through 14 wherein  $R^1$  is optionally substituted alkyl or optionally substituted carbocyclic aryl or optionally substituted aryalkyl.

16. A method of any one of claims 5 through 15 wherein  $R^2$  is optionally substituted carbocyclic aryl or optionally substituted heteroaromatic and heteroalicyclic.

17. A method of any one of claims 5 through 16 wherein X is an optionally substituted alkylene.

18. A method of any one of claims 5 through 16 wherein X is an optionally substituted carbocyclic aryl or an optionally substituted heteroaromatic group.

19. A method of any one of claims 5 through 16 wherein X is an optionally substituted carbocyclic aryl or an optionally substituted heteroalkylene group.

20. A method of any one of claims 5 through 16 wherein X is  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$  or  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$ .

21. A method of any one of claims 5 through 16 wherein X is optionally substituted phenyl, optionally substituted phenoxy; or optionally substituted phenylamino.

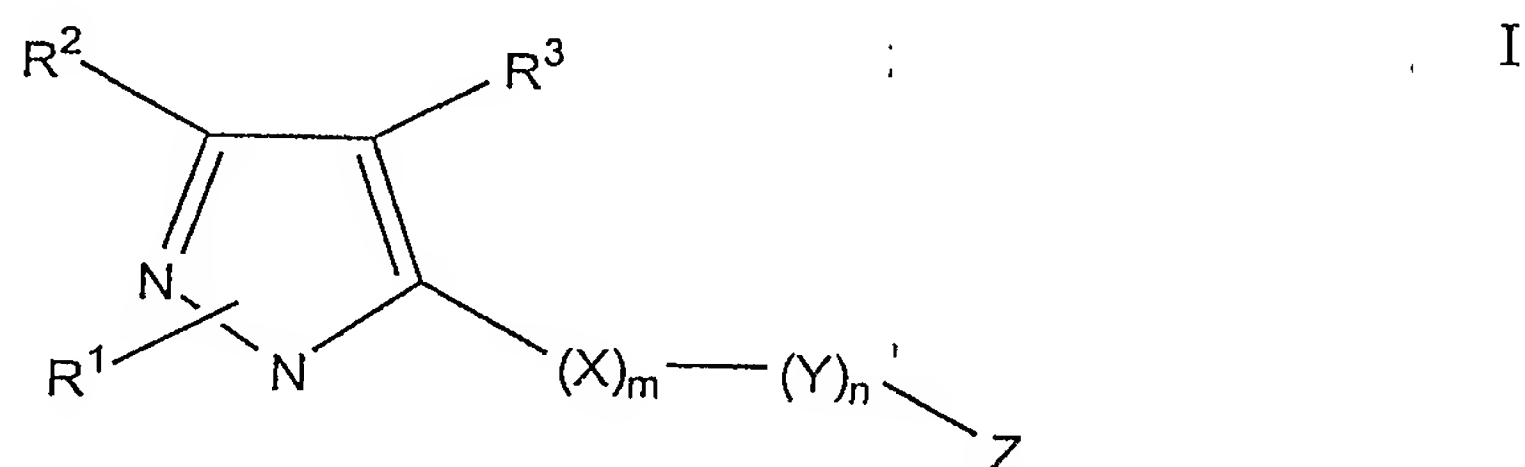
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22. A method of any one of claims 5 through 7 and 13 through 21 wherein Z is a phenolic moiety.

23. A method of any one of claims 5 through 7 and 13 through 21 wherein Z is a tyrosine group.

24. A method for treatment of a subject suffering from or susceptible to a disease or disorder associated with phosphodiesterase PDE4, adenosine transporters, or prostanoid receptors, comprising administering to the mammal a therapeutically effective amount of a substituted pyrazole compound.

25. A method of claim 24 wherein the pyrazole compound is of the following Formula I:



wherein R<sup>1</sup> is hydrogen; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group;

R<sup>2</sup> and R<sup>3</sup> are each independently hydrogen, halogen, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted alkylthio; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group;

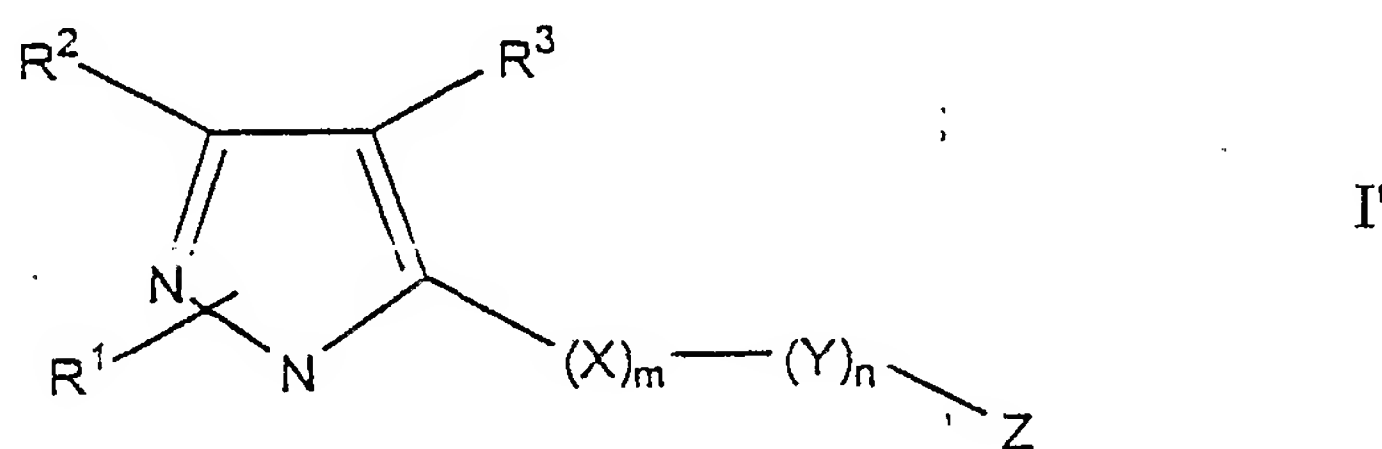
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X is optionally substituted alkylene; optionally substituted alkenylene; optionally substituted alkynylene; optionally substituted heteroalkylene; optionally substituted heteroalkenylene; optionally substituted heteroalkynylene; or X is optionally alicyclic, optionally substituted carbocyclic aryl; optionally substituted heteroalicyclic, optionally substituted heteroaromatic, optionally substituted heteroaralkyl, or optionally substituted heteroalicyclicalkyl group;

Y is optionally substituted amino; optionally substituted methylene; carbonyl; or sulfonyl;

Z is an optionally substituted alkylamine; an amino acid; or a glycine; m is 0 or 1; n is 0 or 1; and pharmaceutically acceptable salts thereof.

26. A method of claim 24 wherein the pyrazole compound is of the following Formula I':



wherein R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are each independently hydrogen; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted alkylthio; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl;

X is optionally substituted alkylene; optionally substituted alkenylene; optionally substituted alkynylene; optionally substituted heteroalkylene; optionally substituted heteroalkenylene; optionally substituted heteroalkynylene; optionally substituted alicyclic; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic; optionally substituted heteroalicyclic group; optionally substituted heteroaralkyl; or optionally substituted heteroalicyclicalkyl group;

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Y is optionally substituted amino; optionally substituted methylene; carbonyl; or sulfonyl;

Z is an optionally substituted alkylamine; an amino acid; or a glycine; m and n are each independently 0 or 1; and pharmaceutically acceptable salts thereof.

27. A method of any one of claims 1 through 26 wherein the compound is selected from the group consisting of:

N-{5-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]pentanoyl}tyrosinamide;  
 N-{5-[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]pentanoyl}tyrosinamide;  
 N-{5-[1-(4-tert-butylphenyl)-5-pyridin-3-yl-1H-pyrazol-3-yl]pentanoyl}tyrosinamide;  
 N-{5-[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]pentanoyl}tyrosinamide;  
 N-{5-[1-(4-tert-butylphenyl)-5-pyridin-4-yl-1H-pyrazol-3-yl]pentanoyl}tyrosinamide;  
 N-{5-[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]pentanoyl}-N,N-dimethyltyrosinamide;  
 N-(3-[1-(4-tert-butylphenyl)-5-pyridin-3-yl-1H-pyrazol-3-yl]propanoyl)tyrosinamide;  
 N-(3-[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]propanoyl)tyrosinamide  
 N-[4-(1-butyl-3-isoquinolin-3-yl-1H-pyrazol-5-yl)benzoyl]tyrosinamide;  
 N-{5-[1-(4-isopropylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]pentanoyl}tyrosinamide;  
 N-{6-[1-(4-isopropylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}tyrosinamide  
 N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}-3-hydroxyphenylalaninamide;  
 N-[1-(aminocarbonyl)-3-(4-hydroxyphenyl)propyl]-5-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]pentanamide;  
 N-[5-(1-butyl-3-isoquinolin-3-yl-1H-pyrazol-5-yl)pentanoyl]tyrosinamide;  
 N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}serinamide;  
 N-{6-[1-(4-iso-propylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}serinamide;  
 N-{6-[1-(4-iso-propylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}threonamide;  
 N-{5-[1-(4-isopropylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]pentanoyl}tyrosinamide;  
 6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]-N-[2-(4-hydroxyphenyl)ethyl]hexanamide;  
 N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}tyrosinamide;  
 N-{5-[1-(4-tert-butylphenyl)-3-isoquinolin-3-yl-1H-pyrazol-5-yl]pentanoyl}tyrosinamide;

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N-{6-[1-(4-tert-butylphenyl)-3-isoquinolin-3-yl-1H-pyrazol-5-yl]hexanoyl}tyrosinamide;  
N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}-N-methyltyrosinamide;  
N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}-4-(hydroxymethyl)phenylalaninamide;  
4-amino-N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}phenylalaninamide;  
4-(acetylamino)-N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}phenylalaninamide;  
4-(aminocarbonyl)-N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}phenylalaninamide;  
N-butyl-N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}tyrosinamide;  
N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}threonamide;  
N-[2-amino-1-(4-hydroxyphenyl)-2-oxoethyl]-6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanamide;  
N-{2-[4-(aminosulfonyl)phenyl]ethyl}-5-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]pentanamide;  
N-({5-[1-(4-isopropylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]thien-2-yl}carbonyl)tyrosinamide;  
N-[2-amino-1-(4-hydroxyphenyl)-2-oxoethyl]-4-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]benzamide;  
4-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]-N-[2-(4-hydroxyphenyl)ethyl]benzamide;  
N-{3-[1-(4-tert-butylbenzyl)-3-isoquinolin-3-yl-1H-pyrazol-5-yl]benzoyl}tyrosinamide;  
N-{5-[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]pentanoyl}tyrosinamide;  
N-{3-[1-(4-tert-butylbenzyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]benzoyl}tyrosinamide;  
N-{3-[1-(4-tert-butylphenyl)-3-isoquinolin-3-yl-1H-pyrazol-5-yl]benzoyl}tyrosinamide;  
N-[4-(1-butyl-3-isoquinolin-3-yl-1H-pyrazol-5-yl)benzoyl]tyrosinamide;  
N-{3-[1-(4-tert-butylbenzyl)-3-quinolin-3-yl-1H-pyrazol-5-yl]benzoyl}tyrosinamide;



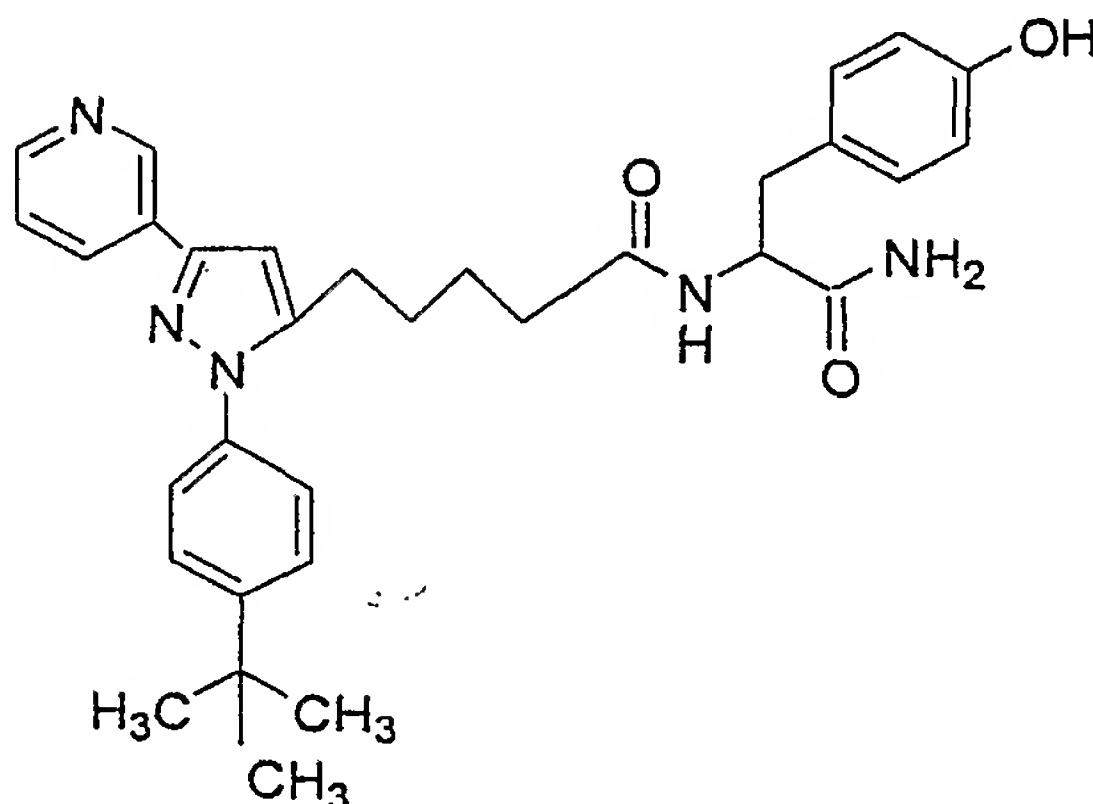
N-{3-[3-isoquinolin-3-yl-1-(4-propylphenyl)-1H-pyrazol-5-yl]benzoyl}tyrosinamide;  
N-{5-[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]pentanoyl}tyrosinamide;  
N-{3-[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]benzoyl}tyrosinamide;  
N-{4-[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]benzoyl}tyrosinamide;  
N-{5-[1-(4-tert-butylbenzyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]pentanoyl}tyrosinamide;  
N-{3-[1-(4-tert-butylbenzyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]benzoyl}tyrosinamide;  
N-{5-[1-(4-tert-butylbenzyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]pentanoyl}tyrosinamide;  
N-{5-[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]pentanoyl}tyrosinamide;  
N-[3-(1-butyl-3-isoquinolin-3-yl-1H-pyrazol-5-yl)benzoyl]tyrosinamide;  
N-(4-{[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]amino}butanoyl)tyrosinamide;  
N-({3-[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]propoxy}acetyl)}tyrosinamide;  
4-[2-({3-[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]propyl}amino)ethyl]phenol;  
N-{3-[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]propyl}tyrosinamide;  
N-acetyl-N-{3-[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]propyl}tyrosinamide;  
N-({3-[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]propoxy}acetyl)tyrosinamide;  
4-[2-({3-[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]propyl}amino)ethyl]phenol;  
N-{3-[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]propyl}tyrosinamide;  
N-acetyl-N-{3-[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]propyl}tyrosinamide;  
3-[(4-{[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]amino}butanoyl)amino]-4-(4-hydroxyphenyl)butanamide;  
N-(4-{[1-(4-tert-butylphenyl)-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-pyrazol-5-yl]amino}butanoyl)tyrosinamide;  
N-(3-{[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]amino}propyl)tyrosinamide;  
N-acetyl-N-(3-{[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]amino}propyl)tyrosinamide;

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N-(4-{[1-(4-tert-butylphenyl)-3-(1-oxidopyridin-4-yl)-1H-pyrazol-5-yl]amino}butanoyl)tyrosinamide;  
4-{[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]amino}-N-[2-(4-hydroxyphenyl)ethyl]butanamide;  
4-{2-[(4-{[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]amino}butyl)amino]ethyl}phenol;  
N-(4-{[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]amino}butanoyl)-N-(2-hydroxyethyl)tyrosinamide;  
N-(4-{[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]amino}butanoyl)-N-[2-(1-methylpyrrolidin-2-yl)ethyl]tyrosinamide;  
N-(4-{[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]amino}butanoyl)tyrosinamide;  
N-(4-{[1-(4-tert-butylphenyl)-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrazol-5-yl]amino}butanoyl)tyrosinamide;  
(3R)-3-[(4-{[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]amino}butanoyl)amino]-4-(4-hydroxyphenyl)butanamide;  
N-(3-{[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]amino}propyl)tyrosinamide;  
N-acetyl-N-(3-{[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]amino}propyl)tyrosinamide;  
N-(4-{[1-(4-tert-butylphenyl)-3-(1-oxidopyridin-3-yl)-1H-pyrazol-5-yl]amino}butanoyl)tyrosinamide;  
4-{[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]amino}-N-[2-(4-hydroxyphenyl)ethyl]butanamide;  
4-{2-[(4-{[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]amino}butyl)amino]ethyl}phenol;  
N-(4-{[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]amino}butanoyl)-N-(2-hydroxyethyl)tyrosinamide;  
N-(4-{[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]amino}butanoyl)-N-[2-(1-methylpyrrolidin-2-yl)ethyl]tyrosinamide;  
N-(4-{[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]oxy}butanoyl)tyrosinamide; or an optical isomer, racemate or tautomer of any one thereof or a pharmaceutically acceptable salt of any one thereof.

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28. A method of any one of claims 1 through 26 wherein the compound is the following:



29. A method of any one of claims 1 through 28 wherein the mammal is a human.

30. A method of any one of claims 1 through claim 29 wherein the mammal is a female.

31. A method of any one of claims 1 through 29 wherein the mammal is a male.

32. A method of any one of claims 1 through 23 or 27 through 30 wherein the mammal is a female suffering from an ovulatory disorder.

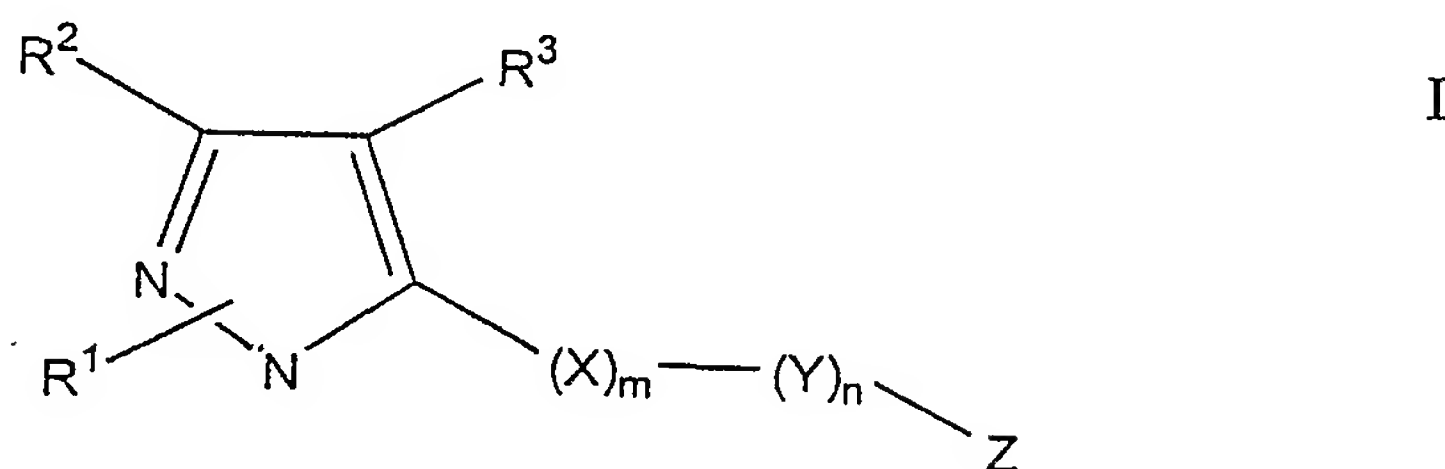
33. A method of any one of claims 1 through 23 or 27 through 30 wherein the mammal is a female being treated with an assisted reproduction procedure.

34. A method of any one of claims 1 through 23 or 27 through 30 wherein the mammal is a female undergoing in-vitro fertilization.

35. A method of any one of claims 1 through 25 or 27 through 29 wherein the mammal is a male suffering from a spermatogenesis disorder.

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36. A compound of the following Formula I:



wherein  $R^1$  is hydrogen; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group;

$R^2$  and  $R^3$  are each independently hydrogen, halogen, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted alkylthio; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group;

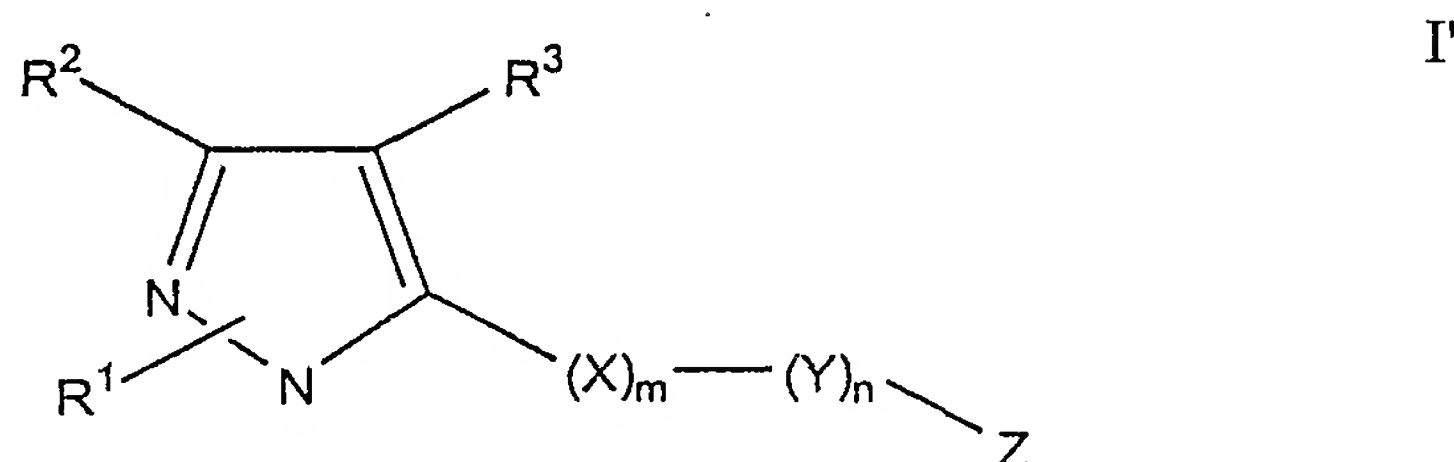
X is optionally substituted alkylene; optionally substituted alkenylene; optionally substituted alkynylene; optionally substituted heteroalkylene; optionally substituted heteroalkenylene; optionally substituted heteroalkynylene; or X is optionally alicyclic, optionally substituted carbocyclic aryl; optionally substituted heteroalicyclic, optionally substituted heteroaromatic, optionally substituted heteroaralkyl, or optionally substituted heteroalicyclicalkyl group;

Y is optionally substituted amino; optionally substituted methylene; carbonyl; or sulfonyl;

Z is an optionally substituted alkylamine; an amino acid; or a glycine; m is 0 or 1; n is 0 or 1; and pharmaceutically acceptable salts thereof.

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37. A compound of the following Formula I':



wherein R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are each independently hydrogen; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted alkylthio; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl;

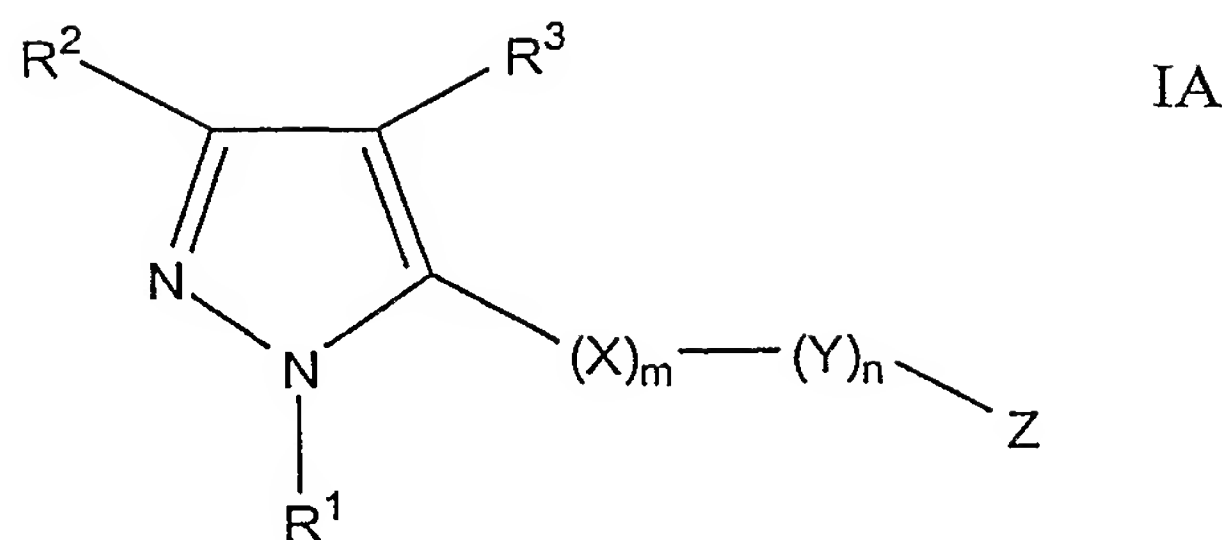
X is optionally substituted alkylene; optionally substituted alkenylene; optionally substituted alkynylene; optionally substituted heteroalkylene; optionally substituted heteroalkenylene; optionally substituted heteroalkenynylene; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic; optionally substituted heteroalicyclic group; optionally substituted heteroaralkyl; or optionally substituted heteroalicyclicalkyl group;

Y is optionally substituted amino; optionally substituted methylene; carbonyl; or sulfonyl;

Z is an optionally substituted alkylamine; an amino acid; or a glycine; m and n are each independently 0 or 1; and pharmaceutically acceptable salts thereof.

38. A compound of claim 36 wherein the compound is of the following Formula IA:

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wherein  $R^1$  is optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted alkylthio; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group;

$R^2$  and  $R^3$  are each independently hydrogen; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted alkylthio; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl;

X is optionally substituted alkylene; optionally substituted alkenylene; optionally substituted alkynylene; optionally substituted heteroalkylene; optionally substituted heteroalkenylene; optionally substituted heteroalkenynylene; optionally substituted carbocyclic aryl, aralkyl, optionally substituted heteroaromatic; optionally substituted heteroalicyclic group; optionally substituted heteroaralkyl; or optionally substituted heteroalicyclicalkyl group;

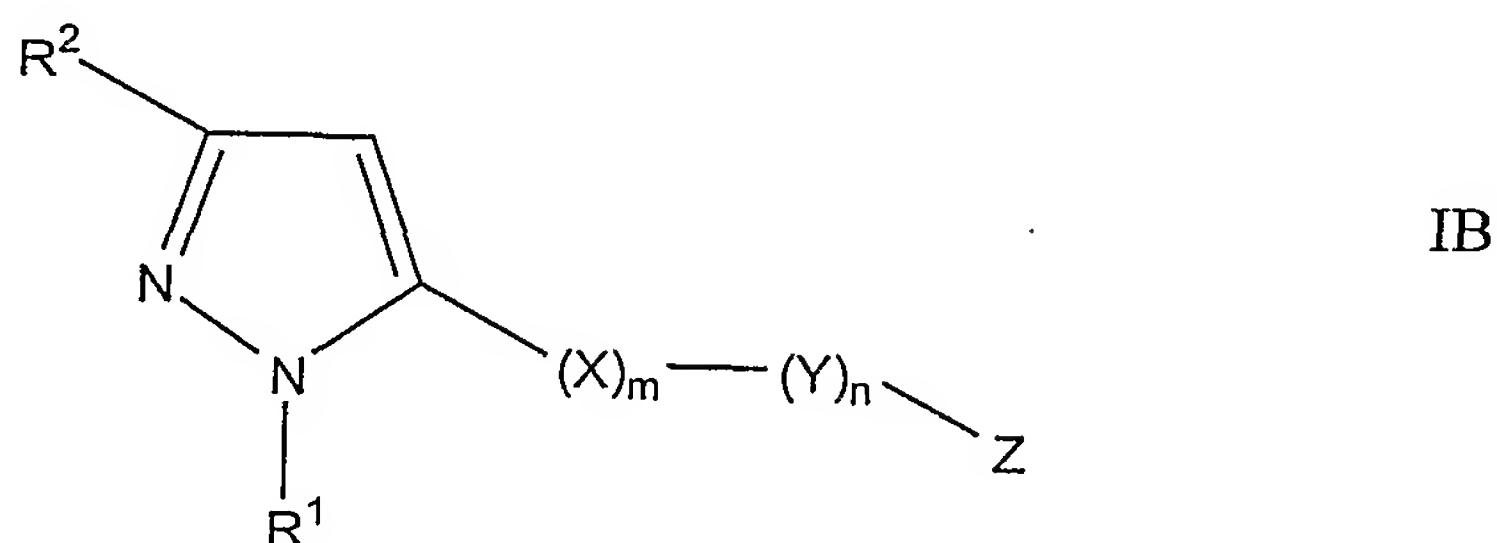
Y is optionally substituted amino; optionally substituted methylene; carbonyl; or sulfonyl;

Z is an optionally substituted alkylamine; an amino acid; or a glycine; m and n are each independently 0 or 1; and pharmaceutically acceptable salts thereof.



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39. A compound of claim 36 wherein the compound is of the following Formula IB:



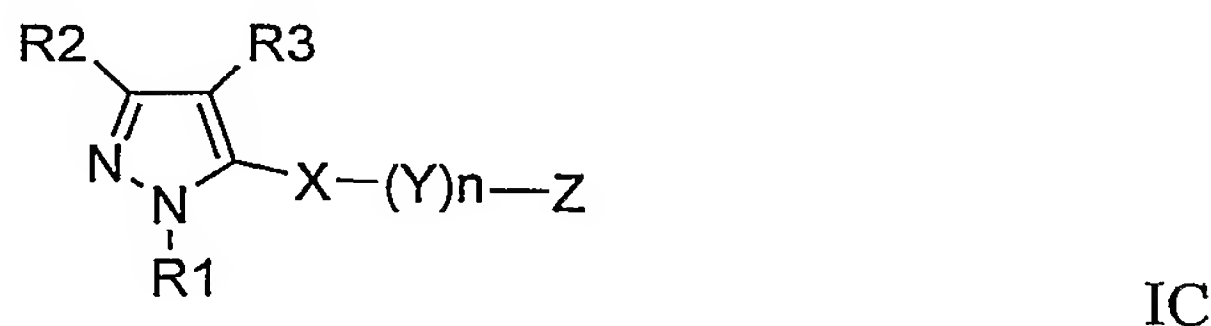
wherein  $R^1$  and  $R^2$  are each independently optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group;

X is optionally substituted alkylene; optionally substituted alkenylene; optionally substituted alkynylene; optionally substituted heteroalkylene; optionally substituted heteroalkenylene; optionally substituted heteroalkenynylene; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic; optionally substituted heteroalicyclic group; optionally substituted heteroaralkyl; or optionally substituted heteroalicyclicalkyl group;

Y is optionally substituted amino; optionally substituted methylene; carbonyl; or sulfonyl;

Z is an optionally substituted alkylamine; an amino acid; or a glycine; m and n are each independently 0 or 1; and pharmaceutically acceptable salts thereof.

40. A compound of claim 36 wherein the pyrazole compound is of the following Formula IC:



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wherein  $R^1$  is hydrogen; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group;

$R^2$  is halogen; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted alkylthio; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group;

$R^3$  is hydrogen; halogen; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted alkylthio; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group;

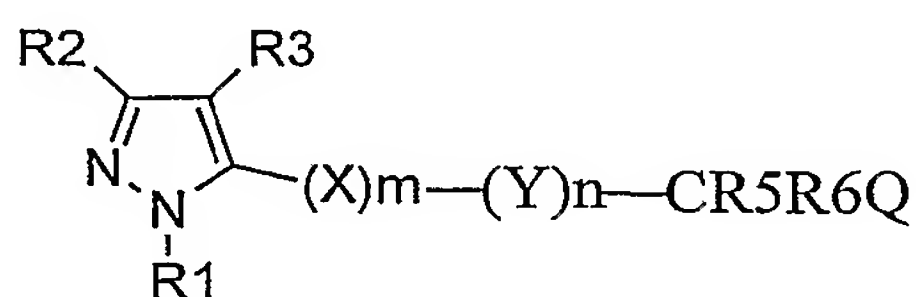
Y is optionally substituted amino; optionally substituted methylene; carbonyl; or sulfonyl;

Z is an optionally substituted alkylamine; an amino acid; or a glycine;

n is 0 or 1;

X is optionally substituted heteroalkylene; optionally substituted heteroalkenylene; optionally substituted heteroalkynylene; and pharmaceutically acceptable salts thereof.

41. A compound of claim 36 wherein the compound is of the following Formula ID



ID

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wherein R<sup>1</sup> is hydrogen; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group;

R<sup>2</sup> is halogen; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted alkylthio; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group;

R<sup>3</sup> is hydrogen; halogen; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted alkylthio; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group;

X is optionally substituted alkylene; optionally substituted alkenylene; optionally substituted alkynylene; optionally substituted heteroalkylene; optionally substituted heteroalkenylene; optionally substituted heteroalkynylene; or X is optionally alicyclic, optionally substituted carbocyclic aryl; optionally substituted heteroalicyclic, optionally substituted heteroaromatic, optionally substituted heteroaralkyl, or optionally substituted heteroalicyclicalkyl group;

Y is optionally substituted amino; optionally substituted methylene; carbonyl; or sulfonyl;

Z is an optionally substituted alkylamine; an amino acid; or a glycine;

n is 0 or 1;

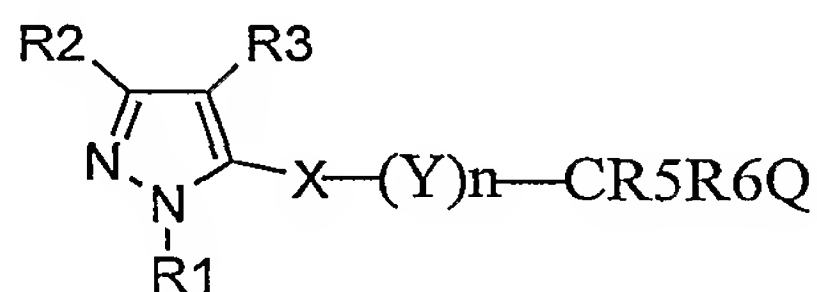
R<sup>5</sup> and R<sup>6</sup> are independently hydrogen, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group;

Q is omitted or is  $-(CH_2)_p-CO-A-R^7$  wherein p is 0, 1 or 2, A is O or NH and R<sup>7</sup> is independently hydrogen, optionally substituted alkyl; optionally substituted

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alkenyl; optionally substituted alkynyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group; and pharmaceutically acceptable salts thereof.

42. A compound of claim 36 wherein the compound is of the following Formula IE



IE

wherein R<sup>1</sup> is optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group;

R<sup>2</sup> is halogen; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted alkylthio; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group;

R<sup>3</sup> is hydrogen; halogen; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted alkylthio; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group;

Y is optionally substituted amino; optionally substituted methylene; carbonyl; or sulfonyl;

Z is an optionally substituted alkylamine; an amino acid; or a glycine;

n is 0 or 1;

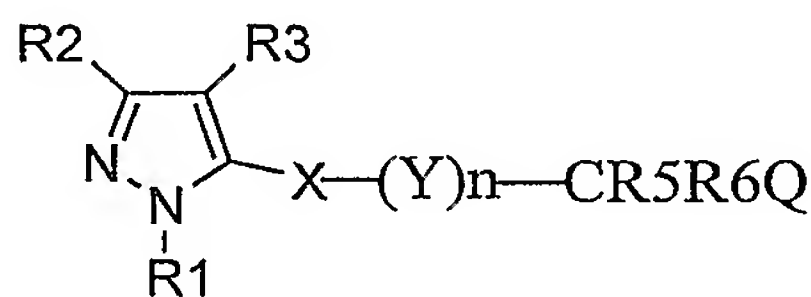
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X is optionally substituted heteroalkylene; optionally substituted heteroalkenylene; optionally substituted heteroalkynylene;

R<sup>5</sup> and R<sup>6</sup> are independently hydrogen; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group; and

Q is omitted or is  $-(CH_2)_p-CO-A-R^7$  wherein p is 0, 1 or 2, A is O or NH and R<sup>7</sup> is independently hydrogen, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group; and pharmaceutically acceptable salts thereof.

43. A compound of claim 36 wherein the compound is of the following Formula IF:



IF

wherein R<sup>1</sup> is optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group;

R<sup>2</sup> is halogen; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted alkylthio; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group;

R<sup>3</sup> is hydrogen; halogen; optionally substituted alkyl; optionally substituted



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alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted alkylthio; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group;

Y is optionally substituted amino; optionally substituted methylene; carbonyl; or sulfonyl;

Z is an optionally substituted alkylamine; an amino acid; or a glycine;

n is 0 or 1;

X is optionally alicyclic, optionally substituted carbocyclic aryl; optionally substituted heteroalicyclic, optionally substituted heteroaromatic, optionally substituted heteroaralkyl, or optionally substituted heteroalicyclicalkyl group;

R<sup>5</sup> and R<sup>6</sup> are independently hydrogen, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group; and

Q is omitted or is  $-(CH_2)_p-CO-A-R^7$  wherein p is 0, 1 or 2 ; A is O or NH and R<sup>7</sup> is independently hydrogen, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclic aryl; optionally substituted aralkyl; optionally substituted heteroaromatic or heteroalicyclic group; or optionally substituted heteroaralkyl or heteroalicyclicalkyl group; and pharmaceutically acceptable salts thereof.

44. A compound of any one of claims 36 through 43 wherein at least one of R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> is other than hydrogen.

45. A compound of any one of claims 36 through 44 wherein R<sup>2</sup> is other than hydrogen.

46. A compound of any one of claims 36 through 45 wherein R<sup>1</sup> is optionally substituted alkyl or optionally substituted carbocyclic aryl or optionally substituted aralkyl.



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47. A compound of any one of claims 36 through 46 wherein R<sup>2</sup> is optionally substituted carbocyclic aryl or optionally substituted heteroaromatic and heteroalicyclic.

48. A compound of any one of claims 36 through 47 wherein X is an optionally substituted alkylene group.

49. A compound of any one of claims 36 through 47 wherein X is an optionally substituted carbocyclic aryl or optionally substituted heteroaromatic group.

50. A compound of any one of claims 36 through 47 wherein X is heteroalkylene.

51. A compound of any one of claims 36 through 47 wherein X is  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$  or  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$ .

52. A compound of any one of claims 36 through 47 wherein X is optionally substituted phenyl, optionally substituted phenoxy, or optionally substituted phenylamino.

53. A compound of claim 36 or 37 wherein the compound is selected from the group consisting of:

N-{5-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]pentanoyl}tyrosinamide;  
N-{5-[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]pentanoyl}tyrosinamide;  
N-{5-[1-(4-tert-butylphenyl)-5-pyridin-3-yl-1H-pyrazol-3-yl]pentanoyl}tyrosinamide;  
N-{5-[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]pentanoyl}tyrosinamide;  
N-{5-[1-(4-tert-butylphenyl)-5-pyridin-4-yl-1H-pyrazol-3-yl]pentanoyl}tyrosinamide;  
N-{5-[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]pentanoyl}-N,N-dimethyltyrosinamide;  
N-(3-[1-(4-tert-butylphenyl)-5-pyridin-3-yl-1H-pyrazol-3-yl]propanoyl)tyrosinamide;  
N-(3-[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]propanoyl)tyrosinamide  
N-[4-(1-butyl-3-isoquinolin-3-yl-1H-pyrazol-5-yl)benzoyl]tyrosinamide;

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N-{5-[1-(4-isopropylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]pentanoyl}tyrosinamide;  
N-{6-[1-(4-isopropylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}tyrosinamide  
N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}-3-hydroxyphenylalaninamide;  
N-[1-(aminocarbonyl)-3-(4-hydroxyphenyl)propyl]-5-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]pentanamide;  
N-[5-(1-butyl-3-isoquinolin-3-yl-1H-pyrazol-5-yl)pentanoyl]tyrosinamide;  
N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}serinamide;  
N-{6-[1-(4-iso-propylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}serinamide;  
N-{6-[1-(4-iso-propylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}threonamide;  
N-{5-[1-(4-isopropylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]pentanoyl}tyrosinamide;  
6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]-N-[2-(4-hydroxyphenyl)ethyl]hexanamide;  
N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}tyrosinamide;  
N-{5-[1-(4-tert-butylphenyl)-3-isoquinolin-3-yl-1H-pyrazol-5-yl]pentanoyl}tyrosinamide;  
N-{6-[1-(4-tert-butylphenyl)-3-isoquinolin-3-yl-1H-pyrazol-5-yl]hexanoyl}tyrosinamide;  
N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}-N-methyltyrosinamide;  
N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}-4-(hydroxymethyl)phenylalaninamide;  
4-amino-N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}phenylalaninamide;  
4-(acetylamino)-N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}phenylalaninamide;  
4-(aminocarbonyl)-N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}phenylalaninamide;  
N-butyl-N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}tyrosinamide;  
N-{6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanoyl}threonamide;  
N-[2-amino-1-(4-hydroxyphenyl)-2-oxoethyl]-6-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]hexanamide;

N-{2-[4-(aminosulfonyl)phenyl]ethyl}-5-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]pentanamide;

N-({5-[1-(4-isopropylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]thien-2-yl}carbonyl)tyrosinamide;

N-[2-amino-1-(4-hydroxyphenyl)-2-oxoethyl]-4-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]benzamide;

4-[1-(4-tert-butylphenyl)-3-pyridin-2-yl-1H-pyrazol-5-yl]-N-[2-(4-hydroxyphenyl)ethyl]benzamide;

N-{3-[1-(4-tert-butylbenzyl)-3-isoquinolin-3-yl-1H-pyrazol-5-yl]benzoyl}tyrosinamide;

N-{5-[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]pentanoyl}tyrosinamide;

N-{3-[1-(4-tert-butylbenzyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]benzoyl}tyrosinamide;

N-{3-[1-(4-tert-butylphenyl)-3-isoquinolin-3-yl-1H-pyrazol-5-yl]benzoyl}tyrosinamide;

N-[4-(1-butyl-3-isoquinolin-3-yl-1H-pyrazol-5-yl)benzoyl]tyrosinamide;

N-{3-[1-(4-tert-butylbenzyl)-3-quinolin-3-yl-1H-pyrazol-5-yl]benzoyl}tyrosinamide;

N-{3-[3-isoquinolin-3-yl-1-(4-propylphenyl)-1H-pyrazol-5-yl]benzoyl}tyrosinamide;

N-{5-[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]pentanoyl}tyrosinamide;

N-{3-[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]benzoyl}tyrosinamide;

N-{4-[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]benzoyl}tyrosinamide;

N-{5-[1-(4-tert-butylbenzyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]pentanoyl}tyrosinamide;

N-{3-[1-(4-tert-butylbenzyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]benzoyl}tyrosinamide;

N-{5-[1-(4-tert-butylbenzyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]pentanoyl}tyrosinamide;

N-{5-[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]pentanoyl}tyrosinamide;

N-[3-(1-butyl-3-isoquinolin-3-yl-1H-pyrazol-5-yl)benzoyl]tyrosinamide;

N-(4-{[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]amino}butanoyl)tyrosinamide;

N-({3-[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]propoxy}acetyl}tyrosinamide;

4-[2-({3-[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]propyl}amino)ethyl]phenol;

N-{3-[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]propyl}tyrosinamide;

N-acetyl-N-{3-[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-

yl]propyl}tyrosinamide;  
N-({3-[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]propoxy}acetyl)tyrosinamide;  
4-[2-({3-[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]propyl}amino)ethyl]phenol;  
N-{3-[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]propyl}tyrosinamide;  
N-acetyl-N-{3-[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]propyl}tyrosinamide;  
3-[(4-{[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]amino}butanoyl)amino]-4-(4-hydroxyphenyl)butanamide;  
N-(4-{[1-(4-tert-butylphenyl)-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-pyrazol-5-yl]amino}butanoyl)tyrosinamide;  
N-(3-{[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]amino}propyl)tyrosinamide;  
N-acetyl-N-(3-{[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]amino}propyl)tyrosinamide;  
N-(4-{[1-(4-tert-butylphenyl)-3-(1-oxidopyridin-4-yl)-1H-pyrazol-5-yl]amino}butanoyl)tyrosinamide;  
4-{[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]amino}-N-[2-(4-hydroxyphenyl)ethyl]butanamide;  
4-{2-[(4-{[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]amino}butyl)amino]ethyl}phenol;  
N-(4-{[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]amino}butanoyl)-N-(2-hydroxyethyl)tyrosinamide;  
N-(4-{[1-(4-tert-butylphenyl)-3-pyridin-4-yl-1H-pyrazol-5-yl]amino}butanoyl)-N-[2-(1-methylpyrrolidin-2-yl)ethyl]tyrosinamide;  
N-(4-{[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]amino}butanoyl)tyrosinamide;  
N-(4-{[1-(4-tert-butylphenyl)-3-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-pyrazol-5-yl]amino}butanoyl)tyrosinamide;  
(3R)-3-[(4-{[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]amino}butanoyl)amino]-4-(4-hydroxyphenyl)butanamide;  
N-(3-{[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-

yl]amino}propyl)tyrosinamide;

N-acetyl-N-(3-{[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]amino}propyl)tyrosinamide;

N-(4-{[1-(4-tert-butylphenyl)-3-(1-oxidopyridin-3-yl)-1H-pyrazol-5-yl]amino}butanoyl)tyrosinamide;

4-{[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]amino}-N-[2-(4-hydroxyphenyl)ethyl]butanamide;

4-{2-[(4-{[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]amino}butyl)amino]ethyl}phenol;

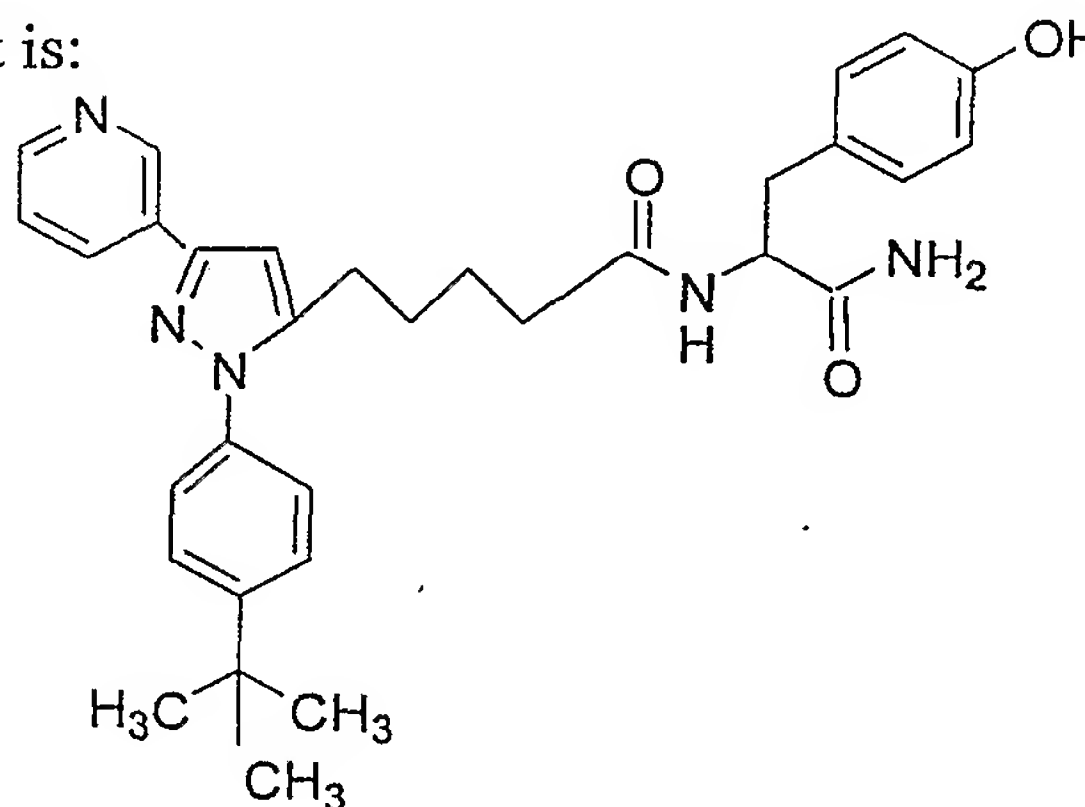
N-(4-{[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]amino}butanoyl)-N-(2-hydroxyethyl)tyrosinamide;

N-(4-{[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]amino}butanoyl)-N-[2-(1-methylpyrrolidin-2-yl)ethyl]tyrosinamide;

N-(4-{[1-(4-tert-butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]oxy}butanoyl)tyrosinamide;

or an optical isomer, racemate or tautomer of any one thereof or a pharmaceutically acceptable salt of any one thereof.

54. A compound that is:



55. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and one or more compounds of any one of claims 36 through 54.

56. A pharmaceutical composition of claim 55 wherein the composition is in an oral dosage form.



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ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.*

(54) Title: USE OF PYRAZOLE DERIVATIVES FOR TREATING INFERTILITY

(57) Abstract: The invention provides substituted pyrazole compounds, and methods of treatment and pharmaceutical compositions that utilize or comprise one or more such compounds. Compounds of the invention are useful for the treatment of mammalian infertility.

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# INTERNATIONAL SEARCH REPORT

In: ational Application No  
PCT/US 01/16189

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 A61K31/415 A61P5/34

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, SCISEARCH, BIOSIS, MEDLINE, EMBASE, PAJ

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 191 147 B1 (PURDY CASEY PRITCHARD ET AL) 20 February 2001 (2001-02-20) page 1, column 1, line 11 - line 24 column 2, line 63 -column 3, line 5 column 9, line 21 - line 54 table III	36-48, 51,55,56
A	WO 98 22101 A (RAZ AMIRAM ;MASFERRER JAIME L (US); SEARLE & CO (US)) 28 May 1998 (1998-05-28) claims 7,8	36-54
X	US 4 833 135 A (EDWARDS PHILIP N ET AL) 23 May 1989 (1989-05-23) page 4, line 57 - line 65 column 7, line 52 - line 57 examples 1,2 claims	1-4, 29-35

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 01/16189

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3 842 088 A (HABECK D ET AL) 15 October 1974 (1974-10-15) column 5, line 37 - line 60 claim 1 -----	1-4, 29-35

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-2729-53,55-56 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Consequently, the search has been restricted to the pyrazole compounds prepared in the examples, and, based on those compounds, to a generalisation of their structural formulae to encompass compounds having the following structural features: a pyrazole substituted with a pyridine in 3, an alkylphenyl group connected to the nitrogen in 1 or 2, and an alkyl portion on the carbon atom in 5.

Claims 24-26 relate to the treatment of diseases which are actually not well defined. The use of the definitions " disorder associated with phosphodiesterase PDE4, adenosine transporters, prostanoid receptors" in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT.

The lack of clarity is such as to render a meaningful complete search not fully possible. Consequently, the search for claims 24-26 has been restricted to the mechanisms claimed.

Claims searched completely: 28,54.

Claims searched incompletely: 1-27,29-53,55,56.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/16189

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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